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THE CLINICAL SIGNIFICANCE OF GALLOP RHYTHM¹

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BOSTON

The confused state of the literature respecting gallop rhythm, the relatively long discussions and the relatively infrequent clinical reports are the occasion for the presentation of this series of 100 cases.

In the first place, the condition has been called by a number of names: first, "*bruit de rappel*" by Bouillaud in 1835, later, in 1875, "*bruit de galop*" by Potain, later still, "*bruit de trot*," and by the English "*canter rhythm*." A strict separation of these different terms, as requested by Bard, is impossible, the types of gallop rhythm merging one into the other and the terms actually designating the same general phenomenon. Gallop rhythm is the expression that has survived, and its general and common adoption indicates its usefulness, even though by strict definition it does not fit all cases. A list of the more important references in the literature to gallop rhythm appears at the end of this paper. Special attention is called to the recent review of the subject by Guiroux and to that by Holt, with their bibliographies.

Gallop rhythm may be most satisfactorily defined as a rapid sequence of three heart sounds with each cardiac cycle. Usually the heart rate is rapid—100 or more—but sometimes even slow gallop rhythm is described with pulse rates as slow as 70.

An attempt has been made to separate gallop rhythm into four types: presystolic, systolic, protodiastolic and mesodiastolic. Sometimes it is possible to fit a given case into one of these groups, especially when the pulse is not fast, but often it is impossible to tell whether the gallop rhythm is protodiastolic, mesodiastolic or presystolic, even with graphic records. For example, let us suppose that there is a presystolic third sound in a given case due to delayed auriculoventricular conduction and coming 0.1 second before the first sound. At a heart rate of 100 and with the interval between the normal first and second sounds of the heart about 0.3 second, there will be 0.2 second between the second and third sounds. The presystolic character of the gallop rhythm in this case should be evident. If, however, the rate is speeded up to 120 or higher, with little or no change in auriculoventricular

¹Read before the American Climatological and Clinical Association, White Sulphur Springs, W. Va., May, 1927.

conduction time or duration of systole (the latter slightly shortened as is the rule with increased heart rate), the position of the third sound relative to the second sound is altered. It falls as near the second sound as the first, or even nearer if the rate is very fast as indicated in figure 1.

Thus with increasing pulse rate, the presystolic gallop becomes at first mesodiastolic and finally even protodiastolic, without appreciable change in its mechanism.

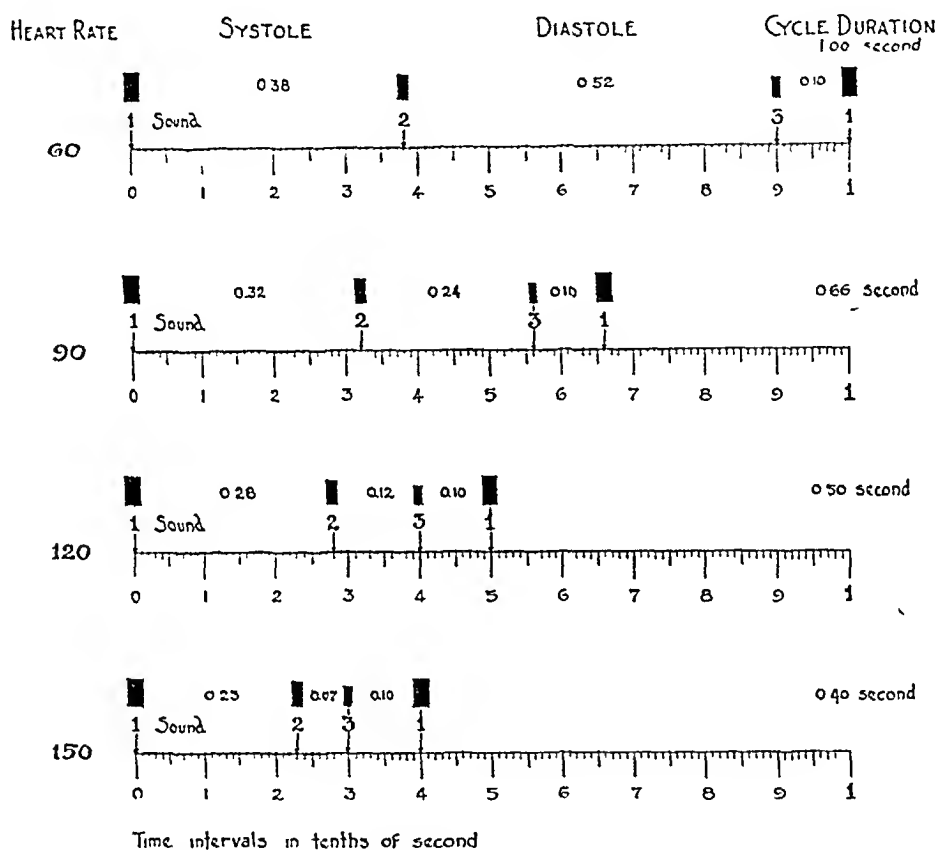


Fig 1—Presystolic gallop rhythm showing the effect of changing heart rate on relative position of the three heart sounds

Similarly the protodiastolic rhythm, which at slower rates may be evident becomes a mesodiastolic gallop with rapid rate (fig 2). Thus it may not be possible to analyze a mesodiastolic gallop rhythm as to fundamental protodiastolic or presystolic character.

The mechanism of gallop rhythm of all varieties is often obscure. Sometimes a delay in auriculoventricular conduction time appears to explain either the presystolic or the protodiastolic gallop rhythm, depending on the degree of heart block and the heart rate but even in the presystolic type no delay in conduction need be present. The third element of the protodiastolic gallop corresponds closely to the third

sound of the heart in time and in character. Whether it is due to the same unknown mechanism causing the normal third sound is not known. It seems to me likely that it is. It may be caused by the opening snap of the auriculoventricular valves under unusually great venous and intra-auricular pressure (from stasis) plus dilatation of the ventricular cavities. It may be the result of vibration of the dilated ventricular walls from the rapid stream of blood entering early in diastole, it may be due to other causes. The mesodiastolic gallop rhythm is apparently either the presystolic or the protodiastolic placed centrally in diastole by the fast

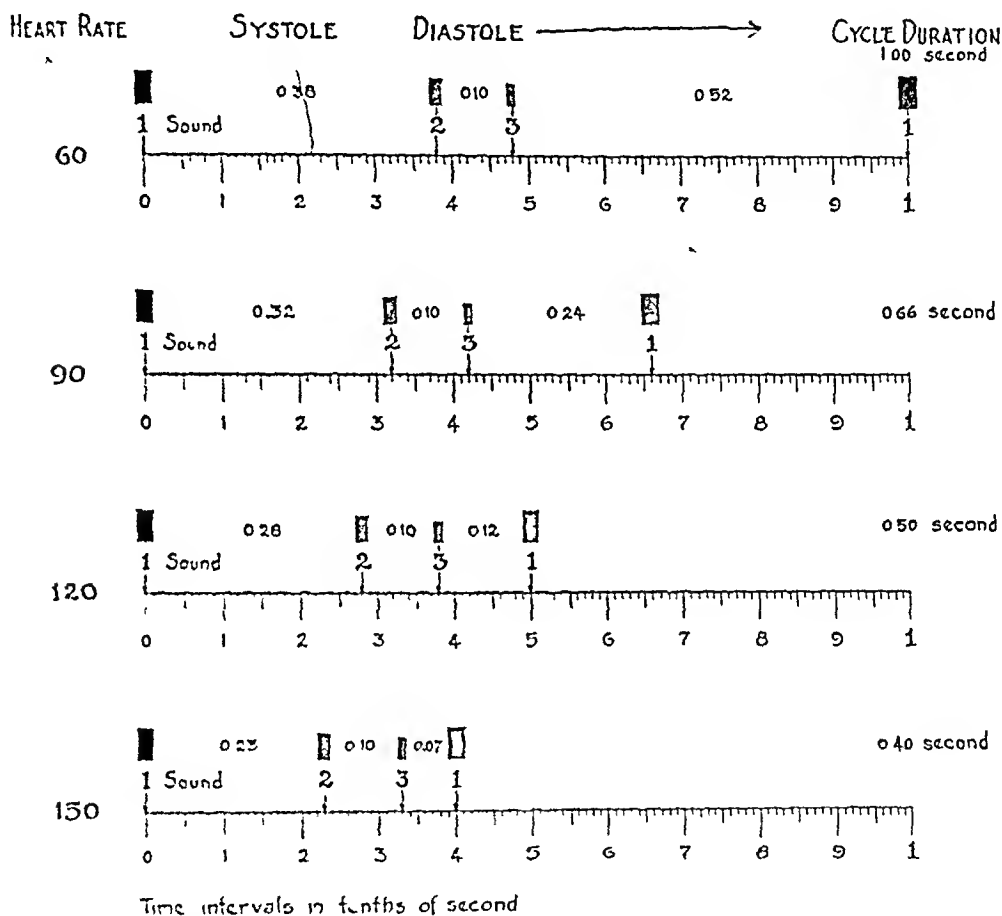


Fig 2—Protodiastolic gallop rhythm, showing the effect of changing heart rate on relative position of the three heart sounds

heart rate, it is probable that there is not actually a mesodiastolic type. In these three timings of the diastolic gallop rhythm the interval of systole is, except in slow pulse rates, considerably longer than either division of diastole, the longest pause is systole. Finally, systolic gallop rhythm is rare and of unknown cause, it has been suggested by Bard and others that it is the result of a dissociation of the muscular and valvular elements of the first sound in cardiac weakness. It may, except by graphic records, be difficult to distinguish from the presystolic gallop rhythm, since it is protosystolic in time.

Gallop rhythm must not be confused with simple rapid reduplication of the heart sounds or with frustrate premature contractions occurring bigeminally, as it not infrequently is by medical men unacquainted with the differentiation, especially in respect to reduplication of the second heart sound

Gallop rhythm is peculiarly an apical phenomenon, although it may be heard better elsewhere, such exceptions are rare. It is frequently associated with a synchronous palpable and visible impulse¹. It is an important sign in the clinic in civilian life, and is almost always of considerable gravity. During the World War, when soldiers with severe effort syndrome were gathered together a combination of marked tachycardia and loud third heart sounds occasioned a minimization of the importance of gallop rhythm widely at variance with the appreciation of the significance of the phenomenon as seen in civilian practice. Even among patients with definite effort syndrome and otherwise normal hearts in civilian life gallop rhythm is relatively rare, in a series of 100 such patients that I examined recently a third sound was well heard in only ten and in only one of those was the rate rapid enough for a diagnosis of gallop rhythm. In such cases differentiation is easily made from the serious gallop rhythm of heart disease in which the extra sound is generally very much louder than the usual third heart sound heard with difficulty by many physicians.

Likewise mitral stenosis with a loud third sound and tachycardia may give rise to gallop rhythm, but not often, chiefly because the third sound is masked by the mitral diastolic murmur that accompanies and follows it.

The typical gallop rhythm is found in serious heart disease associated with hypertension, coronary disease or syphilitic aortitis, and is accompanied by congestive failure. Nephritis is not common although it has been considered in much of the past literature to be an important factor. Gallop rhythm may be found in severe diphtheria. Angina pectoris and coronary thrombosis are common and pulsus alternans not infrequent. Murmurs and valvular disease are uncommon except for slight apical systolic murmurs. The heart is almost always considerably enlarged, and the sounds generally are poor. Auriculoventricular block is uncommon in spite of past theories of auriculoventricular dissociation.

1 Rarely the third sound and impulse associated with it in protodiastolic gallop rhythm may be even more prominent than the usual cardiac sounds and apex impulse, as in ten cases recently reported by Conner, seen by him in the past fifteen years (Conner, L. A. Note on the Occurrence of an Unusual Form of Gallop Rhythm. *Am Heart J* 2: 514 [June] 1927). He writes that in these cases "the gallop sound is so loud and the corresponding palpable shock so strong as to dominate completely the cardiac signs."

Results of Observations in One Hundred Cases of Gallop Rhythm

| | Type of Gallop Rhythm | | | | Total |
|---|-----------------------|-----------------|----------|-----------------|-------|
| | Proto diastolic | Presys tolic | Systolic | Unspeci fied | |
| Total Cases | 64 | 12 | 4 | 20 | 100 |
| Sex | | | | | |
| Male | 47 | 7 | 3 | 15 | 72 |
| Female | 17 | 5 | 1 | 5 | 28 |
| Age | | | | | |
| Under 20 years | 5 | 0 | 0 | 2 | 7 |
| From 20 to 30 years | 5 | 1 | 0 | 3 | 9 |
| From 30 to 40 years | 7 | 1 | 2 | 3 | 13 |
| From 40 to 50 years | 7 | 1 | 1 | 4 | 13 |
| From 50 to 60 years | 18 | 6 | 0 | 4 | 28 |
| From 60 to 70 years | 14 | 2 | 1 | 3 | 20 |
| 70 years and over | 8 | 1 | 0 | 1 | 10 |
| Etiology | | | | | |
| Coronary disease | 14 | 2 | 1 | 2 | 19 |
| Coronary disease plus all complications | 38 | 7 | 1 | 8 | 54 |
| Coronary thrombosis | 13 | 3 | 1 | 4 | 21 |
| Hypertension | 2 | 0 | 0 | 3 | 5 |
| Hypertension plus all complications | 30 | 7 | 1 | 11 | 49 |
| Syphilitic aortitis | 5 | 1 | 0 | 3 | 9 |
| Syphilitic aortitis plus all complications | 9 | 1 | 0 | 3 | 13 |
| Rheumatic heart | 9 | 0 | 0 | 1 | 10 |
| Rheumatic heart plus all complications | 10 | 0 | 1 | 1 | 12 |
| Congenital | 1 | 0 | 0 | 0 | 1 |
| Uremia | 0 | 0 | 0 | 1 | 1 |
| Uremia plus hypertension | 5 | 2 | 0 | 2 | 9 |
| Irritable heart | 0 | 1 | 1 | 1 | 3 |
| Subacute bacterial endocarditis | 2 | 0 | 0 | 0 | 2 |
| Nephritis | 6 | 2 | 0 | 4 | 12 |
| Pericarditis | 1 | 0 | 1 | 1 | 3 |
| Unknown | 2 | 1 | 1 | 1 | 5 |
| Duration of illness | | | | | |
| Under 1 year | 15 | 5 | 1 | 2 | 23 |
| From 1 to 5 years | 23 | 4 | 1 | 6 | 34 |
| More than 5 years | 12 | 3 | 0 | 1 | 16 |
| ? | 14 | 0 | 2 | 11 | 27 |
| Congestive Failure | 42 | 5 | 1 | 13 | 61 |
| Angina Pectoris | 18 | 4 | 1 | 2 | 25 |
| Cardiac Asthma | 6 | 3 | 0 | 3 | 14 |
| Pulse Rate | | | | | |
| Under 80 | 4 | 0 | 0 | 0 | 4 |
| From 80 to 100 | 25 | 6 | 3 | 6 | 40 |
| From 100 to 120 | 24 | 3 | 1 | 7 | 35 |
| 120 and over | 6 | 3 | 0 | 3 | 12 |
| ? | 5 | 0 | 0 | 4 | 9 |
| Blood Pressure—Systolic | | | | | |
| Under 100 mm | 2 | 1 | 0 | 0 | 3 |
| From 100 to 150 | 27 | 3 | 3 | 10 | 43 |
| From 150 to 200 | 24 | 5 | 1 | 5 | 35 |
| From 200 to 250 | 10 | 3 | 0 | 5 | 18 |
| 250 and over | 1 | 0 | 0 | 0 | 1 |
| Pulsus Alternans | 13 | 5 | 0 | 3 | 21 |
| Size of Heart | | | | | |
| Very large | 18 | 0 | 1 | 8 | 27 |
| Moderate enlargement | 23 | 3 | 1 | 6 | 33 |
| Slight enlargement | 5 | 6 | 1 | 4 | 16 |
| Normal | 1 | 3 | 1 | 1 | 6 |
| Doubtful | 17 | 0 | 0 | 1 | 18 |
| Heart Sounds | | | | | |
| Poor | 34 | 5 | 1 | 12 | 52 |
| Fair | 16 | 5 | 0 | 3 | 24 |
| Good | 9 | 2 | 1 | 2 | 14 |
| ? | 5 | 0 | 2 | 3 | 10 |
| Murmurs and Valve Lesions | | | | | |
| Aortic regurgitation | 8 | 1 | 1 | 5 | 15 |
| Mitral stenosis | 3 | 0 | 0 | 1 | 4 |
| Both aortic regurgitation and mitral stenosis | 4 | 0 | 0 | 0 | 4 |
| Apical systolic, loud | 9 | 0 | 0 | 3 | 12 |
| Apical systolic, slight or moderate | 21 | 2 | 1 | 6 | 33 |
| No murmurs | 16 | 9 | 2 | 5 | 32 |
| Electrocardiogram | | | | | |
| Total | 43 | 8 | 2 | 11 | 64 |
| Normal | 2 | 0 | 0 | 0 | 2 |
| Auriculoventricular block | 8 | 2 | 0 | 1 | 11 |
| Intraventricular block | 16 | 2 | 1 | 5 | 24 |

Results of Observations in One Hundred Cases of Gallop Rhythm—Continued

| | Type of Gallop Rhythm | | | | Total |
|--|-----------------------|-------------|----------|-------------|-------|
| | Proto-diastolic | Presystolic | Systolic | Unspecified | |
| Ectopic auricular tachycardia | 2 | 2 | 0 | 1 | 5 |
| Abnormal T wave | 10 | 2 | 0 | 4 | 16 |
| Low voltage | 4 | 0 | 0 | 0 | 4 |
| Left axis deviation abnormal | 12 | 3 | 1 | 3 | 19 |
| Auricular fibrillation | 2 | 0 | 2 | 1 | 5 |
| Ventricular premature beats alone | 7 | 2 | 0 | 2 | 11 |
| Auricular premature beats alone | 2 | 0 | 0 | 0 | 2 |
| Both auricular and ventricular premature beats | 5 | 1 | 0 | 0 | 6 |
| Nonprotein Nitrogen in Blood | | | | | |
| Normal amount | 8 | 1 | 2 | 4 | 15 |
| Abnormal amount | 2 | 0 | 0 | 3 | 5 |
| Renal Function (phenolsulphonphthalein) | | | | | |
| Normal | 4 | 2 | 1 | 1 | 8 |
| Abnormal | 5 | 0 | 0 | 4 | 9 |
| Digitalis | | | | | |
| Large amount | 9 | 0 | 0 | 3 | 12 |
| Moderate or little | 23 | 5 | 1 | 8 | 47 |
| None | 15 | 5 | 3 | 9 | 32 |
| | 7 | 2 | 0 | 0 | 9 |
| Dead | | | | | |
| Total | 31 | 3 | 1 | 14 | 49 |
| Within one week after the discovery of the gallop rhythm | 3 | 1 | 0 | 2 | 6 |
| From 1 week to 1 month | 4 | 0 | 0 | 5 | 9 |
| From 1 to 6 months | 12 | 1 | 1 | 3 | 17 |
| From 6 to 12 months | 7 | 0 | 0 | 2 | 9 |
| From 1 to 2 years | 4 | 0 | 0 | 0 | 4 |
| From 2 to 3 years | 1 | 1 | 0 | 0 | 2 |
| 3 years and over | 0 | 0 | 0 | 2 | 2 |

as a frequent cause of the gallop. Intraventricular block, almost always of the right bundle branch type, is more common, but by no means uniform, simply representing extensive myocardial disease. The heart rhythm is almost always normal, except that there are frequent premature beats. Auricular fibrillation is rare. The pulse rate is usually between 80 and 120 and rarely above or below these limits. Males more often show the phenomenon than females. The sign is one of bad omen, when occurring in the clinic it usually means death within a few years at best; there are exceptions. Digitalis therapy is apparently not related to gallop rhythm, except that improvement in the cardiac condition from its use may cause the gallop rhythm to disappear, and occasionally delayed conduction from digitalization may give rise to temporary presystolic or even, if extreme, protodiastolic gallop rhythm.

PRESENT OBSERVATIONS

A series of 100 cases of gallop rhythm observed during the last few years has been analyzed and the results recorded in the accompanying table. Sixty-five patients from my own private practice were studied; two from that of Dr. H. B. Sprague and thirty-three from the wards and outpatient department of the Massachusetts General Hospital.²

² In the study of the hospital patients, I wish to acknowledge the assistance of Dr. Seeley G. Mudd and Miss Catharine Thacher.

An attempt was made to divide them into four groups, (1) presystolic, twelve cases, (2) systolic, four cases, (3) protodiastolic, sixty-four cases, and (4) uncertain, mostly mesodiastolic, twenty cases. No great accuracy can be attached to this subdivision. The total data of the entire series of 100 cases are of considerable significance and are the basis, together with data from the literature, for the description of the typical gallop rhythm described in the foregoing paragraphs. Phonocardiograms were not taken in this series, they would be of interest in the attempt to time and to differentiate more accurately the various so-called types. Electrocardiograms were made in sixty-four of the cases.

SUMMARY AND CONCLUSIONS

1 An analysis has been made of 100 patients with gallop rhythm seen in private and in hospital practice.

2 The differentiation of these cases into types according to the time of the extra or third sound showed sixty-four apparently protodiastolic, twelve presystolic, four systolic and twenty unclassified. The exact separation of protodiastolic and presystolic types is often difficult or impossible. With rapid heart rates, as 120, the position of the third sound in diastole is practically the same, i. e., mesodiastolic, whether protodiastolic or presystolic with slower rates. The systolic type is rare and much less important apparently than the diastolic types which are about equally significant. The commonest type, namely, the protodiastolic, is probably due to the marked accentuation of the usually faint normal third heart sound.

3 Gallop rhythm is an important clinical sign in civilian practice, and is almost invariably evidence of serious heart disease. It is generally a bad prognostic sign, almost half of the 100 patients in the present series (45 per cent) are known to have died within two years of the discovery of the sign, thirty-two died within six months. A considerable number of the remaining fifty-five patients were seriously ill or dead (4) when last heard from. Cases of gallop rhythm of the protodiastolic, presystolic and unclassified diastolic types were all represented in this high mortality, but less of the presystolic than the others.

4 In the entire group of 100 cases, males were more often affected than females, in the proportion of about three to one.

5 Gallop rhythm occurred in both young and old. In sixteen patients under 30 years of age, it was more often associated with nephritis or mitral stenosis, and in the older patients with coronary disease, hypertension and syphilitic aortitis. The average age was between 50 and 60 years. One half of the patients (48 per cent) were between 50 and 70.

6 In the group of 100 cases, coronary disease alone or in combination was apparently present in 54 per cent, actual coronary thrombosis

being diagnosed in 21 Hypertension alone or complicated was present in 49 per cent, syphilitic aortitis in 13 per cent, rheumatic heart disease in 12 per cent, nephritis in 12, uremia in 10, effort syndrome alone in 3, pericarditis in 3, subacute bacterial endocarditis in 2, congenital heart disease in 1 and unknown factors in 5

7 The duration of the heart disease before the discovery of the gallop rhythm was variable, often brief but still more often of several years' standing

8 Congestive failure was the most outstanding characteristic, being present in at least 61 per cent

9 Angina pectoris was a common occurrence (25 per cent)

10 Cardiac asthma occurred in fourteen cases

11 The heart rate was usually rapid, averaging about 100 At least three fourths of the cases showed rates between 80 and 120

12 The blood pressure was variable, the systolic being between 100 and 150 mm of mercury in 43 per cent, between 150 and 200 in thirty-five cases, over 200 in nineteen, and under 100 in three

13 Pulsus alternans was frequently found (21 per cent)

14 The heart was considerably enlarged in 60 per cent, definitely normal in size in only 6, and doubtful in 18

15 The heart sounds were poor in more than half the cases (52 per cent) and good in only fourteen

16 Valvular disease was uncommon, aortic regurgitation being found alone in fifteen cases, mitral stenosis alone in four and the two conditions combined in four Apical systolic murmurs, however, were common, loud in twelve and slight to moderate in thirty-three There were no heart murmurs in thirty-two cases

17 Electrocardiograms were obtained in sixty-four of the patients Only two of these were normal Abnormal T waves were present in sixteen, low voltage in four, abnormal left axis deviation in nineteen, auricular fibrillation in only five, ectopic auricular tachycardia in five, ventricular premature beats alone in eleven, auricular premature beats alone in two and both auricular and ventricular premature beats in six Intraventricular block was the most common electrocardiographic abnormality found, occurring in twenty-four cases, or 38 per cent, but auriculoventricular block was surprisingly infrequent, being recorded in only eleven cases

18 Renal function as tested by the phenolsulphonphthalein test was normal in eight and abnormal in nine of the seventeen cases so tested The amount of nonprotein nitrogen in the blood was normal in fifteen and too high in only five of the twenty cases in which such tests were made

19 Digitalis as a possible factor in the production of gallop rhythm was negligible, as shown by the fact that in at least thirty-two cases none had been given and in only twelve cases had a considerable amount been administered. As a matter of fact, in some cases the gallop rhythm disappeared coincidently with the clinical improvement following rest and the administration of digitalis.

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ALKALIS AND RENAL INJURY

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It has long been an established clinical fact that diuresis may be produced by the administration of alkalis¹ M Fischer emphasized the theoretical consideration that accumulation of water in tissues was due to an increased tissue acidity² For some time therapy in nephritis and in albuminurias has been directed toward alkalinization of the urine Post and Thomas³ claimed decidedly beneficial results with this therapy in orthostatic albuminuria A thorough review of this literature is unnecessary It suffices to emphasize that in certain edematous states therapy with alkalis of various sorts has yielded a diuresis, but in certain cases has caused a dangerous exacerbation of the edema

With the development of more accurate methods of study of the hydrogen ion concentration of the blood, and of the status of the alkali reserve in the presence of an acidosis, it has further been demonstrated that a diminished reserve of the fixed bases frequently occurs in nephritic states with or without edema⁴ Rehn⁵ believed that disturbance of renal tubular activity inhibited excretion of acids, while the excretion of alkali was dependent on glomerular function His data are almost purely clinical and not fully controlled An acidosis, both actual and relative, exists in acute infections⁶ and anaphylactic shock. However Hirsch has shown⁷ that the nephritis which may be produced by sodium acid phosphate is not due to the acidosis These data tend to confirm the impression that water retention is sometimes associated with an accumulation of acid The voluminous literature dealing with the relation of the chlorides to edema is most conflicting and confusing

1 Palmer, W T, and Henderson L J J Biol Chem **21** 37, 1915

2 Fischer, M H Oedema and Nephritis, New York, John Wiley & Sons, 1915

3 Post, W E and Thomas, W Orthostatic Albuminuria, J A M A **80** 293 (Feb 3) 1923

4 Bulger H A Peters, J P Eisenman, A J, and Lee, C J Clin. Investigation **2** 167, 1926 *ibid* **2** 233, 1925 Chloride in Diabetic Acidosis, editorial J A M A **86** 752 (March 13) 1926 Chace, A F, and Myers, V C Acidosis in Nephritis, J A M A **74** 641 (March 6) 1920

5 Rehn, E Ztschr f Urol **19** 27, 1925

6 Dragstedt, L R J Infect Dis **27** 452, 1920 Hirsch, E F *Ibid.* **28** 275, 1921 *ibid* **29** 40, 1921 Hirsch, E F, and Williams, J L *Ibid* **30** 259, 1922, *ibid*, **30** 664 1922

7 Hirsch, E F Hydrogen-Ion Studies, Experimental Nephritis in Rabbits with Monoblastic Sodium Phosphate, Arch Int Med **31** 862 (June) 1923

some authors⁸ claiming good therapeutic results by complete and radical restriction of chlorides, and others not

In view of the conception that water retention is associated with an increased tissue acidity, the therapeutic use of acid substances in edema, with excellent results, seems most paradoxical. Keith, Barrier and Whelan⁹ produced clinical diuresis with calcium chloride, with a positive urinary calcium balance and a great increase in the sodium content of the urine. These observations have been confirmed abroad.¹⁰ Calcium chloride has been found¹¹ to increase the urinary acidity and may even lead to a severe uncompensated acidosis,¹² but is still diuretic. Similar results occur with ammonium sulphate and ammonium chloride.¹³ The diuretic effect is enhanced by the use of merbaphen (novarsurol).¹⁴ Singer¹⁵ laid particular stress on the effect of the calcium on the heart, but Segall and White¹⁶ have demonstrated that the degree of diuresis is dependent on the degree of acidosis.

Andrews¹⁷ has recently pointed out that the liberation of the maximum amount of water from the tissues does not occur until the plasma bicarbonate reserve has fallen to 45 per cent by volume, in normal dogs. The work of Aldrich and McClure and others¹⁸ has shown the

8 Conayou. *Bull Acad de med* **94** 955, 1925

9 Keith, N. M., Barrier, C. W., and Whelan, M. Treatment of Nephritis and Edema with Calcium, *J. A. M. A.* **83** 666 (Aug. 30) 1924

10 Blum, L., Aubel, E., and Hausknecht, R. *Bull et mem Soc med d hôp de Paris* **46** 206, 1922

11 Benatt and Handel. *Klin Wchnschr* **3** 162, 1924. Keith, N. M., Barrier, C. W. and Whelan, M. Diuretic Action of Ammonium Chlorid and Novasurol in Cases of Nephritis with Edema. *J. A. M. A.* **85** 799 (Sept. 12) 1925. Atchley, D. W., Loeb, R. F., and Benedict, E. M. Physicochemical Studies of Calcium Chlorid Diuresis, *ibid* **80** 1643 (June 2) 1923

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13 Gamble, J. L., Blackfan, K. D. and Hamilton, B. *J. Clin. Investigation* **1** 359, 1925. Haldane, J. B. S. *J. Physiol.* **55** 265, 1921

14 Rowntree, L. G., Keith, N. M. and Barrier, C. W. Novasurol in Treatment of Ascites in Hepatic Diseases, *J. A. M. A.* **85** 1187 (Oct. 17) 1925. De Mello-Campos, O. *Sciencia med* **3** 389, 1925

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16 Segall, H. N., and White, P. D. *Am. J. M. Sc.* **170** 647, 1925

17 Andrews, E. Water Metabolism, *Arch. Int. Med.* **37** 83 (Jan.) 1926, Water Metabolism, Further Observations, *ibid*, **37** 559 (April) 1926

18 Aldrich, C. A. and McClure, W. B. Time Required for Disappearance of Intradermally Injected Salt Solution. *J. A. M. A.* **82** 293 (July 28) 1923, Intradermal Salt Solution Test, Its Prognostic Value in "Nephritis" with Generalized Edema, *ibid* **83** 1425 (May 3) 1924. Aldrich, C. A. Clinical Course of Generalized Edema, with Suggestions as to Its Possible Function, *ibid* **84** 481 (Feb. 14) 1925. Baker, W. Intradermal Salt Solution Test in Scarlet Fever and Diphtheria Patients, *ibid* **83** 1566 (Nov. 15) 1924. Olmstead, H. C. Intradermal Salt Solution Test in Cardiac Disease in Children, *Arch. Int. Med.* **37** 281 (Feb.) 1926

presence of a greatly increased avidity of the tissues for water in edematous and pre-edematous states, emphasizing the importance of changes in the tissues rather than merely in the kidneys Clausen¹⁹ and Kaboth²⁰ have shown that in edema significant changes occur in the surface tension and colloidal osmotic pressure of the blood McLean²¹ reviewed the chaos of conceptions concerning edema Labbe and Violle²² contend that edema is due to a combination of factors, namely osmotic balance, acid-base balance, blood minerals and blood lipoids and colloids Hamzlik²³ emphasizes the importance of the nervous apparatus in this connection, Rountree and Brown²⁴ have demonstrated that a true hydropic plethora with edema may be induced by the excessive administration of water, but that this has no relation to true diuresis

Wilson,²⁵ in reviewing the literature, emphasizes that the mechanism of maintaining the neutrality of the body is dependent on the loss of volital carbon dioxide from the lungs, excretion of nonvolital acids and bases by way of the kidneys, excretion of some salts by way of the bowel and the normal buffer substances of the blood, chiefly sodium bicarbonate The effect of perspiration is minor in normal persons The loss of carbon dioxide by way of the lungs is an important factor and is directly controlled by the fact that increasing hydrogen ion concentration is an effective stimulus to the respiratory center²⁶

The mechanism by which the kidney assists in this process is the question most applicable here Henderson's²⁷ and Henderson and Palmer's²⁸ studies have shown that the strong (actively ionized) acids are eliminated as salts, with associated depletion of the fixed metallic cations of the blood However, ammonia, replaces these metallic cations in the urine to a great extent, and therefore tends to spare the alkali

19 Clausen J Biol Chem **59** 45, 1924

20 Kaboth, G Arch f Gynak **127** 170, 1925

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22 Labbe, M, and Violle, P L Ann de med **18** 22, 1925

23 Hamzlik, P J California & West Med **24** 33, 1926

24 Brown, G E, and Rowntree, L G Volume and Composition of Blood, and Changes Incident to Diuresis in Cases of Edema, Arch Int Med **35** 129 (Jan) 1925 Rowntree, L G Physiol Rev **2** 116 1922 Water Enough, More, or Less, editorial, J A M A **86** 1912 (June 19) 1926

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26 Winterstein Arch f d ges Physiol **138** 167, 1911, Biochem Ztschr **70** 45, 1915 Hasselbach Ibid **46** 403, 1912 Anoxemia and Acidosis, Current Comment, J A M A **85** 979 (Sept 26) 1925 Ellis, A W M Quart J Med **17** 405, 1924

27 Henderson, L J Ergebn d Physiol **8** 254, 1909, J Biol Chem **9** 403, 1911

28 Henderson L J, and Palmer W T J Biol Chem **21** 37, 1915

reserve Previous to the work of Nash and Benedict²⁹ the major portion of the urinary ammonia was presumed to arise by destruction of urea in the liver Their researches demonstrated that most of the urinary ammonia is synthesized by the renal tissue Therefore, the acidosis associated with nephritis may at least in part be the result of the failure of proper ammonia synthesis by the kidneys The urinary ammonia is always greatly increased in the presence of an increased secretion of acids,³⁰ and diminished by the administration of alkali³¹

The normal kidney apparently can cope with excesses of alkali more readily if sufficient water is available for the solution of the sodium bicarbonate (maximum concentration is three-tenths normal)³² The fact that alkalization of the urine and the body requires an increased excretion of water is essentially synonymous to diuresis Increased excretion of alkalis may be produced either by physiologic excessive administration of alkalis, or by depletion of acids, as in severe vomiting³³

Out of this chaos of fact and theory, a few salient phenomena are conspicuous First, water metabolism, as exemplified by normal balance, edema or dehydration, is not solely an evidence of altered renal function as regards the excretion of the water, but is greatly influenced by physiologic and chemical conditions of the tissues as a whole Secondly, the acid-base balance of the body is of major importance in the control of a normal equilibrium Thirdly, the kidney, through its selective secretion of either an acid or an alkaline urine, and through its synthesis of ammonia, plays an essential rôle in the maintenance of such equilibrium Therefore, one again returns to the kidneys for an adequate explanation of the paradoxical response in diuresis, sometimes with acid and sometimes with alkali Renal functions are multiple In thinking of edema and renal function one tends to emphasize unduly the function of water elimination, ignoring the renal activity in controlling the reaction of the tissue fluids

The probable mechanism of renal secretion in connection with the control of urinary reaction has been demonstrated³⁴ This was accomplished by the use of nontoxic, sensitive, indicator dyes, introduced into the circulation, and the renal tissue was studied immediately after

29 Nash and Benedict *J Biol Chem* **48** 463, 1921, *ibid* **51** 183, 1922

30 Walter *Arch f exper Path u Pharmacol* **7** 148, 1877 Keeton, R *J Biol Chem* **49** 411, 1921

31 Janney *Ztschr f physiol Chem* **77** 199, 1911 Davis, Haldane and Kennaway *J Physiol* **54** 32, 1920

32 Marchall *J Biol Chem* **51** 3, 1922 Gamble *Ibid* **51** 295, 1922

33 McCann, J *J Biol Chem* **35** 553, 1918 MacCallum et al *Bull Johns Hopkins Hosp* **31** 1, 1920 Hastings, Murray and Murray *J Biol Chem* **46** 223, 1921

34 Stieglitz, E J *Histologic Hydrogen-Ion Studies of Kidney*, *Arch Int Med* **33** 483 (April) 1924

removal It was shown that in the normal animal the cellular reaction of the secreting tissue, namely, the cells of the convoluted tubules and the loops of Henle, was invariably opposite to that of the urine If the urine is acid, the cells are distinctly alkaline in reaction, whereas with an alkaline urine an acid reaction exists in the living cells Any increase in the alkalinity of the urine is accompanied by an increased cellular acidity It was concluded that the reaction of the urine was determined by secretion of an excess either of acid or of alkali by these cells, with the probable retention within the cells of either the cations or the anions, resulting in the observed reversed reaction These results are clearly interpreted in view of Donnan's equilibrium Furthermore, in nephritic kidneys, the injured cells are acid in reaction,³⁴ as is the urine Alkalinization of the urine in nephritic animals does not reverse the acid reaction of the cells, but probably increases the intracellular acidity Similar experiments have since been carried out, using different alkalis, with the same results However, triple calcium phosphate failed to alkalinize the urine, even in massive doses in the acute experiments

Studies with indicator dyes in living tissues such as those already mentioned and those of Rous,³⁵ must be carried out as rapid, acute procedures, and be carefully controlled The results of Rous are in part nullified by the fact that the dye was left in the tissues for a considerable time Organic dyes, particularly the indicators, are salts, and therefore combine with the amphoteric proteins, giving false reactions if left too long in contact For example, sodium alizarinate, if put in contact with egg albumin, will slowly show an acid reaction (alizarin), because the sodium reacts with the amphoteric protein The actual hydrogen ion concentration is unaltered, but the indicator gives a false appearance of acidity However, in the acute experiments referred to previously, this fact was considered

The importance of these phenomena has been insufficiently emphasized Since Fischer² and others³⁶ pointed out the importance of the tissues as a whole in contrast to the kidney in controlling water balance, the pendulum of attention has perhaps swung too far After all, water elimination, and therefore control of water balance, is dependent to a great degree on proper renal secretory activity, either directly, as regards the actual excretion of water, or indirectly through the regulation of tissue neutrality by the kidneys The actual secreting mechanism lies

35 Rous, P J Exper Med 18 183, 1913, Science 60 363, 1924, J Exper Med 41 379, 451 and 739, 1925 Tissue Acidosis, editorial, J A M A 85 519 (Aug 15) 1925 Rous, P, and Drury, D R Outlying Acidosis, *ibid* 85 33 (Jul 4) 1925

36 Footnotes 18, 19 and 21

within the renal cell, and it is important to consider the vital physiologic processes there ³⁷

Recently, Hartman, Bolliger and Doub ³⁸ in studying the physiologic process of roentgen-ray nephritis in dogs showed that during the period of acute reaction with marked albuminuria, the urine was strongly alkaline. In the absence of any systemic or metabolic disease or fever, this alkalinity may be explained only by the local inflammatory acidity of the cells, confirming the earlier experimental data. Peterson and Willis ³⁹ have pointed out that increased hydrogen ion concentration leads to an increased permeability, whereas a diminution in permeability follows diminishing hydrogen ion concentration. This adds emphasis to the conception that alterations in the reaction of the urine have functional physiologic significance.

Excessive administration of alkali has been shown to lead to renal injury ⁴⁰. Nuzum and his associates ⁴¹ showed that long continued alkalinization caused a moderate hypertension and renal damage, but no arteriosclerosis. Addis and others ⁴² have been able to cause a considerable nephritis in rats by prolonged dietary alkalinization with sodium bicarbonate. The recent report of Jordan ⁴³ has brought forth with new emphasis the problem of alkalosis as encountered in the management of peptic ulcers by the Sippy method. As has been previously pointed out by others, ⁴⁴ long continued clinical use of alkalis not infrequently leads to evidence of clinical nephritis and alkalosis. Jordan points out that

37 Stieglitz, E. J. *Am J Anat* **29** 33, 1921

38 Hartman, F. W., Bolliger, A., and Doub, H. P. *Functional Studies Throughout Course of Roentgen-Ray Nephritis in Dogs*, *J A M A* **88** 139 (Jan 15) 1927

39 Peterson, W. F., and Willis, D. A. *Capillary Permeability and Inflammatory Index of Skin in Normal Person as Determined by Blister*, *Arch Int Med* **38**.663 (Nov 26) 1926

40 Henderson, L. J., Palmer, W. W., and Newburgh, L. H. *J Pharmacol and Exper Therap* **5** 449, 1914. Fischer (footnote 2)

41 Nuzum, F. R., Seegal, B., Garland, R., and Osborne, M. *Arteriosclerosis and Increased Blood Pressure, Experimental Production*, *Arch Int Med* **37** 733 (June) 1926

42 Addis, T., MacKay, E. M., and MacKay, L. I. *J Biol Chem* **71** 157, 1926

43 Jordan, S. M. *Calcium Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalis*, *J A M A* **87**. 1905 (Dec 4) 1926

44 Hardt, L. J. and Rivers, A. B. *Toxic Manifestations Following Alkaline Treatment of Peptic Ulcer*, *Arch Int Med* **31** 171 (Feb) 1923. Brown, G. E., Eusterman, G. B., Hartman, H. R., and Rowntree, L. G. *Toxic Nephritis in Pyloric and Duodenal Obstruction, Renal Insufficiency Complicating Gastric Tetany*, *Arch Int Med* **32** 425 (Sept) 1923. Ellis, A. W. M. *Quart J Med* **17** 405, 1924. Houghton, L. W., Venables, J. F., and Loyd, N. L. *Guy's Hosp Rep* **75** 149, 1925. McVicar, C. S. *Tr Am Gastro-Enterol Ass* **27** 230, 1924

there need be no evidence of previous gross renal damage. This is in accord with the explanation offered, namely, that the nephritis is the result, not the cause, of the alkalosis. The excessive dryness and the early rise in the concentration of the nitrogenous waste in the blood are probably the results of dehydration, or essentially synonymous, excessive diuresis, due to the irritation of acidified renal cells.

The phenomenon of alkalosis may occur without alkali therapy in those cases with obstructing ulcers and continuous secretion of acid which is lost by vomiting.⁴⁵ Normally, the blood of the portal vein has a higher alkali reserve than the arterial blood,⁴⁶ probably through the depletion of acid by the gastric mucosa. This is similar to the difference between the blood entering and that leaving the kidneys, the latter having a higher carbon dioxide combining power than the former.

On the basis of a correlation of the foregoing experimental and clinical data the paradox of diuresis by either acidification or alkalization is open to logical physiologic interpretation. Any deviation from normal physiologic physical or chemical conditions, if the deviation is not so excessive as to be destructive, is a stimulant for activity on the part of the cells to return toward the normal environment.⁴⁷ The significant fact is that either procedure, administration of acids or alkalis, causes a deviation from the pre-existing state, and therefore acts as a renal stimulant. The result of renal stimulation is diuresis. Injured cells, already hyperirritable, are more readily influenced. In nephritis the acid renal cells are made more acid by the administration of alkalis, and it is suggested that this added insult is in part responsible for the clinical diuresis so obtained. If the original injury is severe, the additional insult, instead of being stimulating, may be destructive or injurious, with acute exacerbation of the nephritic or toxic edema, as is so often the case.² On the other hand, therapy with acid substances in nephritis tends to more strongly acidify the urine and to diminish the intracellular acidity, bringing the cells closer to their normal state. Such is the tentative explanation of the physiologic paradox of diuresis as the result of either acidification or alkalization therapy, which is offered as a working hypothesis and as being food for thought along these lines. The effect of the improvement of renal function on the tissues is probably through the control which the kidney exercises over the acid-base balance of the body.

The clinical phenomena demonstrated by studies of patients with alkalosis coincide entirely with this conception. Alkalosis, by forcing

45 Ambard, L., Schmidt, F., and Arnoljevitch. *Bull et mem Soc méd d hop de Paris* **51** 75, 1927.

46 Chavil, A. J. *Arch f d ges Physiol* **214** 331, 1926.

47 Childs, C. M. *Individuality in Organisms*. University of Chicago Science Series 1915.

the secretion of a strongly alkaline urine, greatly increases the renal cellular acidity and by such irritation causes renal damage Koehler⁴⁸ has recently pointed out that acidosis is associated with dehydration, whereas in alkalosis there is evidence of increased tissue hydration and a gain in weight If long continued this acidification of the normally alkaline secreting cells may lead to an actual nephrosis This probably does not occur more frequently because of the tremendous reserve of renal structure and physiologic efforts at compensation White,⁴⁹ in a recent discussion of the rational treatment of gastric ulcer, emphasizes the fact that excessive use of alkalis is largely unnecessary Similarly, Loevenhart and Crandall⁵⁰ suggest calcium carbonate in preference to sodium bicarbonate in ulcer therapy, because of its lesser effect on the acid-base balance of the body This is particularly true of patients with pre-existing renal disease The administration of large doses of alkalis in nephritis is theoretically contraindicated, even in the presence of an uncompensated acidosis So far as is known, there is not any physiologic foundation for the use of alkalis in orthostatic albuminuria

SUMMARY

1 Alkalinization of the urine by administration of alkalis causes an increasing renal cellular acidity

2 This reversal of intracellular reaction is undoubtedly physiologically irritating, and thereby frequently produces a renal diuresis

3 The diuresis resulting from acid therapy in nephritis probably results, at least in part, from physiologic neutralization of the renal secreting cells, with improvement of their functional efficiency

4 An alkalosis, as may be produced by long continued or excessive administration of alkalis, causes distinct renal irritation and occasionally a true nephrosis

5 Renal injury may result in impairment in the function of neutrality control and thereby affect the tissues as a whole

6 An explanation of the paradoxical diuresis occurring after therapy with either alkalis or acids is offered

48 Koehler, A E J Biol Chem **72** 99, 1927

49 White, F W Am J M Sc **173** 629, 1927

50 Loevenhart, A S, and Crandall, L A Calcium Carbonate in Treatment of Gastric Hyperacidity Syndrome and in Gastric and Duodenal Ulcer, J A M A **88** 1557 (May 14) 1927

THE IODINE-STARCH TEST OF BODY FLUIDS

DEDUCTIONS FROM OVER ONE HUNDRED CONSECUTIVE TESTS OF
THE EXTERNAL SECRETION OF THE PANCREAS IN DIABETES,
IN DISEASES OF THE GALLBLADDER AND PANCREAS
AND IN A NORMAL CONDITION*

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Considerable interest has been awakened concerning a test for pancreatic activity which has been advanced recently¹ Communications from different sources show its adoption as a clinical procedure for judging the condition of the pancreas by estimating the amylolytic power of its external secretion Doubts have arisen and the number of researches and experiences have multiplied until it seems warranted to present further data on the test

The factors of the combining power of iodine solutions of peptone and other organic substances were known to me before the presentation of the test So far as a solution of peptone admixture was concerned my co-workers and I guarded against this shortly after the test was advanced which was several months before the time of publication of the article by a procedure which I shall mention Because the other factors could not be controlled (they were judged as insignificant), the modification of Piersol Bockus and Shay² was welcomed These observers devised a means of estimating separately all such factors as might be present a matter which seemed most desirable, especially in that it was scientifically appealing and seemingly of advantage in making the test more accurate

CONTROL OF RETURN OF PEPTONE SOLUTION

In the first place, one must make certain, by the use of the fluoroscope, that the tip of the duodenal tube is definitely in the duodenum Other means of judging this are not accurate enough for the test After the injection of 75 or 100 cc of solution of peptone (which should be done slowly so that the solution will not flow back into the stomach), a

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1 Bassler A Quantitative Test of Digestive Pancreatic Activity, Easily Applied Clinically, Tests for Volume of Pancreatic Juice and Bile Secretions, Arch Int. Med 35:162 (Feb) 1925

2 Piersol, G M Bockus, H L, and Shay, H H Value of Starch-Iodine Reaction as a Test of Pancreatic Function, Arch Int. Med 37 431 (March) 1926

jet of air is sent through the tube to drive out the solution of peptone which would be held in it by capillary attraction. The tube is then clamped off for at least three minutes, 30 cc of sterile water is then run through the tube, air is blown through it again, and the tube is clamped off for five more minutes before aspiration for a specimen is begun.

The duodenum is capable of handling only a small amount of fluid at a time, and if this is injected too quickly, there is danger not only of fluid entering the stomach, but of its being residual in the duodenum for several minutes. The latter is a result of three factors: a delay to onward transit at the duodenojejunal angle, reverse peristalsis in the duodenum and a static state in the duodenum from quick distention, which lasts a few seconds.

When the aforementioned technic is used, a confusing return of peptone rarely occurs, this makes the procedure as suggested a satisfactory routine for clinical work, as my experience has shown. Since I adopted this method two years ago, it has been unsatisfactory in but one instance, in that case the duodenum was widely dilated from obstruction in the third part. For all practical purposes one may take it for granted that if the tube is cleared as mentioned, the fluids injected slowly, the duodenum given time to empty itself before aspiration for the specimen is begun and enough pancreatic juice obtained for testing, a specimen is secured in which the factor of the return of peptone can be eliminated.

The next suggestion that Piersol and his co-workers made was that secretions from the duodenum itself contain a diastatic ferment that would interfere with an accurate estimation of the pancreas. There is no doubt that the succus entericus from the duodenum is of considerable volume and, like all fluids of the body, must contain iodine-combining factors. Its diastatic power, however, has never been proved, and it is reasonable to assume that its combining power is not greater than that of bile or any of the other fluids of the body. At present it seems impossible to devise a means to obviate this or even to prove its presence. The starch-iodine method for work on the body fluid in estimating diastatic ferments, which I shall present later, needs considerable revision.

Doubt was then expressed concerning the practical value of the test, this is brought out more by Piersol's method of estimation, in which the iodine-combining factors which are used separately bring one back to these authors' basis of suggesting this modification and the means employed to accomplish it.

After the modification was advanced, all the returns from cases were examined by two procedures, that is, the original method was used, and then the correction of this method by separate estimation of the iodine-

combining factors and by calculation of the result accordingly. As a considerable number of fluids were to be observed, it became advisable to have a schedule so that the modification could be made more quickly, therefore the schedule given in table 1 was employed for the purpose.

Records of more than 1,400 cases in which tests were made before the modification was employed showed a striking difference in results

TABLE 1—*Additions of Iodine for the Bassler Test (According to Piersol et al) in Estimating Iodine-Combining Factors in Duodenal Returns in Amounts of Centimeters of Twenty-Fifth Normal Solution of Iodine Required to Take Care of the Usual One Drop (0.05 cc) Plus the Correction for Combining Factors*

| Number of Bassler Tube | Number of Tube (Piersol et al) | | | | | | | | | |
|------------------------|--------------------------------|-------|--------|-------|--------|-------|-------|-------|--------|-------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 10 | 0.06 | 0.07 | 0.08 | 0.09 | 0.10 | 0.11 | 0.12 | 0.13 | 0.14 | 0.15 |
| 9 | 0.061 | 0.072 | 0.083 | 0.094 | 0.105 | 0.116 | 0.127 | 0.138 | 0.149 | 0.16 |
| 8 | 0.0625 | 0.075 | 0.0875 | 0.10 | 0.1125 | 0.125 | 0.137 | 0.15 | 0.1625 | 0.175 |
| 7 | 0.064 | 0.078 | 0.092 | 0.106 | 0.12 | 0.134 | 0.148 | 0.162 | 0.176 | 0.19 |
| 6 | 0.067 | 0.084 | 0.101 | 0.118 | 0.135 | 0.152 | 0.169 | 0.186 | 0.203 | 0.22 |
| 5 | 0.07 | 0.09 | 0.11 | 0.13 | 0.15 | 0.17 | 0.19 | 0.21 | 0.23 | 0.25 |
| 4 | 0.075 | 0.10 | 0.125 | 0.15 | 0.175 | 0.20 | 0.225 | 0.25 | 0.275 | 0.3 |
| 3 | 0.083 | 0.116 | 0.149 | 0.182 | 0.215 | 0.248 | 0.281 | 0.314 | 0.347 | 0.38 |
| 2 | 0.1 | 0.15 | 0.20 | 0.25 | 0.30 | 0.35 | 0.40 | 0.45 | 0.50 | 0.55 |
| 1 | 0.15 | 0.25 | 0.35 | 0.45 | 0.55 | 0.65 | 0.75 | 0.85 | 0.95 | 1.05 |

TABLE 2—*List of Twenty Consecutive Cases in Which the Original Bassler Test and the Piersol et al Modification Were Performed*

| Case | Bassler Original Units | Piersol Achromie Number of Tubes | Bassler-Piersol Revised (Units) |
|------|------------------------|----------------------------------|---------------------------------|
| 1 | 10 | 2 | 0 |
| 2 | 10 | 2 | 0 |
| 3 | 4 | 1 | 0 |
| 4 | 20 | 3 | 4 |
| 5 | 20 | 1 | 0 |
| 6 | 20 | 1 | 0 |
| 7 | 20 | 2 | 0 |
| 8 | 20 | 2 | 0 |
| 9 | 20 | 2 | 0 |
| 10 | 20 | 2 | 0 |
| 11 | 20 | 2 | 0 |
| 12 | 0 | 2 | 0 |
| 13 | 6 | 1 | 0 |
| 14 | 10 | 2 | 0 |
| 15 | 16 | 3 | 0 |
| 16 | 2 | 1 | 0 |
| 17 | 20 | 4 | 0 |
| 18 | 4 | 1 | 0 |
| 19 | 20 | 3 | 6 |
| 20 | 16 | 3 | 0 |

The records of the first twenty cases in which the modification was used served amply to discourage further attention to the modification (table 2).

It is apparent from a glance at the negative figures in the third column of results as compared to that in the first and from the inconsistencies in practically all of the results that the only deductions possible are either that the original method is in error the Piersol et al modifica-

tion proving it, or that the Piersol modification is in error. Therefore, this modification was not of any value in this work and if depended on would lead only to hopeless and nullified results. I cannot explain the positive unit readings in the Piersol column in cases 4 and 19, but it must be plainly evident that these are made negative by the others in which a 20 unit reading is also found when the original method was used and no units when the modification was used. In such an indirect method of obtaining specimens for examination and in a test of this kind, there are so many factors impossible of control that the modified readings, as in cases 4 and 19, are liable to be worthless. Observations made by myself and my co-workers, however, as well as the experience of others with the Piersol et al modification, prove that uniformly negative or low unit results are obtained, and since there was so much clinical value in the cases studied and examined by the original method, investigations were made to determine the reasons for the failure of the Piersol modification.

IODINE AS A COMBINING SUBSTANCE

Iodine is found in practically all animal, vegetable and marine life. Conspicuous with the halogens, it possesses a remarkable ability to combine readily with nonmetallic (organic) and almost all of the metals forming iodine compounds. This affinity is so strong that even with water it will combine with the hydrogen molecule and form hydriodic acid on standing. When in practically its pure form (aqueous or alcoholic solutions) and in contact with any tissues or products of them, its penetrability and combining power are well known. The products derived from the duodenum are complex, almost all of the organic materials possessing an iodine-combining power. Iodine unites with maltose and dextrose (the end-sugars of the digestion of starches and sugars) with the greatest affinity, with the dextrans somewhat less and with starch the least of all, yet iodine will detect the presence of starch in aqueous solution in only 1 in 400,000 parts, which of course works inversely when starch is used to detect the presence of free iodine.

BOILED STARCH AS A STABLE SUBSTANCE FOR TESTING DIASTASE

In its dry state, starch is a stable substance, the same may be said when it is suspended in cold water before it has had time to hydrolyze and before the granules have been more or less broken up. When the starch granule is broken by heating in water, the tegumentary portion (amidon) automatically undergoes more or less conversion into the dextrans. This is due to a chemical modification of the original starch brought about by the combined agencies of water and heat, to which changes may occur due to the enzymes which are contained in the

incasement of the starch granule and which are not destroyed by heat, or which become active again on cooling. It is true that water and heat generate a starchy substance which rather quickly changes in part into the dextrans, however, the amount of starch in such a solution that is sensitive to iodine is sufficient for a sensitive test. When a converting substance like amyllopsin or diastase is present, however, the conversion is more rapid. Of especial interest is the fact that an enzyme converts only a certain portion of the starch, so that such a solution contains all of the substances from starch to the end-sugars (or the achro-odextrans), and thus the color that results ranges from the characteristic blue with iodine to no color with the dextrans and the sugars, the latter of which have the greater combining power. When small quantities of iodine are added to such a solution, the sugars and the dextrans take it up first, it is not until they are saturated that a blue color is seen on the starch, which is always present in the solution. Of further interest is the fact that the iodine-starch combination as it breaks down into the dextrans will give the iodine to the dextrin (or the sugar), thus the color will gradually fade, and unless more iodine is added, blue is not produced on the starch present.

The facts mentioned in the two foregoing paragraphs caused much confusion in the early days of the test and explain the statement made by Piersol and his associates, namely, that "a marked variation in the reaction could be produced by varying the amount of iodine added." It is strange, therefore, that since they knew this fact, they did not utilize it for recognition in the modification they suggested, and that they arranged the modification by adding these extra amounts of iodine, thus defeating the purpose they desired to achieve. Any variation in the test must not include additional amounts of iodine in the tubes used in the original test. No more than one drop of twenty-fifth normal solution of iodine should ever be added to the tubes, which subsequent data will prove further. The iodine-combining factors may be estimated separately, and with the test performed as originally planned, a method of computation may be devised that would obviate this factor of error, but this method must be one which does not necessitate the addition of more iodine to the original tubes. As will be shown presently, even then it is doubtful that any procedure which employs starch with iodine to estimate iodine-combining substances, other than enzyme activity (which has factors of error in itself), will be valueless.

ORIGINAL TEST ON SUBSTANCES OTHER THAN PANCREATIC JUICE

It may now be in order to report some of my early observations and some that have been made recently. It has long been believed that a diastatic ferment pervades the body generally and is present in all of its

fluids and tissues With the bile of cows, Piersol and others proved that positive readings could be made on the bile with the original iodine-starch test (a matter which is confirmed subsequently) Tests were made of the various constituents in concentrations as they occur in the bile of human beings, as it was hoped that one or more of them might be identified in special ways The results in the original and modified test, as given in table 3, prove that the main constituents of bile do not have a combining or converting power

Various tests were then made on the bile of a number of freshly slaughtered animals and of persons on whom operations had been performed In order to understand these figures, it must be remembered that the bile employed was always the concentrated form contained in gallbladders, in which there was much mucin and coloring matter (both of which have high iodine-combining powers), it was not like the bile

TABLE 3—*Results in Estimating Iodine-Combining Powers of Constituents of Bile in Solutions*

| Substance | Piersol et al Achromic Tubes | Bassler Units |
|--|---------------------------------|------------------|
| Cholesterol, 0.06 per cent solution | None | 0 |
| Lecithin, 0.03 per cent solution | None | 0 |
| Glycocholic acid, 0.63 per cent solution | None | 0 |
| Sodium glycocholate, 0.30 per cent solution | None | 0 |
| Sodium taurocholate, 0.30 per cent solution | None | 0 |
| Artificial bile containing parts in 100: bile salts, 0.93 per cent (consisting of glycocholate 0.63 per cent, taurocholate 0.3 per cent), cholesterol, 0.06 per cent, and lecithin 0.03 per cent, all rendered alkaline with 1.5 per cent sodium bicarbonate in a 1.5 solution | None | 0 |

in the duodenum, especially the diluted form found in a specimen obtained during the test There is no known test or method for the estimation of the amount of mucin, the hydrometer is valueless in maintaining an estimation on the basis of specific gravity, no matter how viscid or thin the specimen may be It is possible that tests of viscosity would have been of some assistance, but they were not made, therefore, the only value of the unit readings was to prove that the mucin and other organic substances, because of the high iodine-combining powers, would give such high readings The tests were made particularly to get an idea of this combining power and to compare it with that of other body fluids, to compare the results obtained with the original test and with the modification of this test and to prove or disprove a point that was raised by Lyon³ that substances from the pancreas might be mixed with the bile while it is still in the biliary tract.

These observations prove that bile, like other body fluids, contains iodine-combining substances, again the inconsistencies between the modification and the original test are shown by the fact that normally there

3 Lyon Personal communication to the author

no pancreatic juice admixture in the biliary system (because if there were sugar would have been formed), and by two important observations which will be presented later. Other substances in fresh normal specimens were tested with the results shown in tables 5, 6 and 7.

It must be remembered that blood serum from human beings contains large amounts of organic substances it contains blood sugar and no doubt the greatest amount of diastase with the exception of the pancreatic juice. The high values are no doubt due to the iodine-combining substances other than diastase. Work has been done in order to

TABLE 4—Results in Estimating Iodine Combining-Power of Natural Biles

| Source | 1 Cc. Bile 4 Cc. 0.5% Starch Solution Sugar Present | Peters et al. Acrometric Tube | Bassler Method Revised, Results in Units | Original Bassler Method Estimated Without 30 Minutes' Incubation Results in Units | Bassler (Original) Estimated Without 30 Minutes' Incubation Results in Units After Standing 20 Minutes | Original Bassler Method Estimations Made in Units After 30 Minutes Incubation and Standing 20 Minutes |
|---------|--|--|---|--|---|--|
| | | | | | | |
| Man A | Negative | 2 tubes | 0 | 20 | 20 | 20 |
| B | Negative | 2 tubes | 0 | 20 | 20 | 20 |
| Pig A | Negative | 2 tubes | 0 | 10 | 20 | 20 |
| B | Negative | 2 tubes | 0 | 8 | 12 | 20 |
| Sheep A | Negative | 1 tube | 6 | 8 | 18 | 20 |
| B | Negative | 1 tube | 4 | 10 | 6 | 10 |
| Cow A | Negative | 1 tube | 0 | 6 | 10 | 16 |
| B | Negative | 1 tube | 0 | 10 | 18 | 20 |

TABLE 5—Pancreatic (Bassler) Test of Blood Serum from Human Beings

| Case | Regular 30 Minute Incubation | Incubation 60 Minutes |
|------|---------------------------------|--------------------------|
| 1 | 18 | 20 |
| 2 | 20 | 20 |
| 3 | 20 | 20 |
| 4 | 18 | 18 |
| 5 | 20 | 20 |
| 6 | 20 | 20 |
| 7 | 20 | 20 |
| 8 | 20 | 20 |

estimate the proportions by precipitating the proteins and by estimating the sugar and the suggestion is that the enzyme factor in the test is about one fourth of the figures shown in table 5.

Normal feces contain approximately 10 per cent albumin, carbohydrates and fats. The material cast off from the walls of the alimentary canal (mucus cells etc.) with the food albumins and sometimes sugar could easily account for these figures. A trivial amount of diastase ferment is probably contained in feces; there is no way, however to estimate this. If it is present (this is as doubtful as its presence in urine), it does not represent more than one third of the figures shown in table 6.

The low figures shown in table 7 represent chiefly iodine-combining factors (bilirubin, cast off cells, cylindroids, leukocytes, urates and others) It is believed that if diastatic enzyme is present, which is more than doubtful, it is so trivial as not to show in the test

PANCREATIC JUICE IN THE DUODENAL RETURN

The results obtained when employing the Piersol modification, sometimes because the proper strength and amount of iodine solution to be added have not been estimated carefully or the possibility of a peptone

TABLE 6—*Pancreatic (Bassler) Test of Fresh Human Feces (5 Gm Solid Feces Macerated in 10 cc Normal Physiologic Sodium Chloride)*

| Case | Piersol et al Achromic Tubes | Bassler Revised | Bassler With no Incubation, Read Immediately | Bassler With no Incubation, Read After Standing 20 Minutes | Bassler With 30 Minute Incubation, Read After Standing 20 Minutes |
|------|------------------------------------|--------------------|--|---|--|
| 1 | 1 tube | 0 | 4 | 6 | 6 |
| 2 | 1 tube | 0 | 0 | 2 | 2 |
| 3 | 0 tube | 2 | 0 | 2 | 2 |
| 4 | 1 tube | 0 | 4 | 8 | 8 |
| 5 | 1 tube | 0 | 0 | 2 | 6 |
| 6 | 0 tube | 0 | 0 | 2 | 4 |
| 7 | 1 tube | 4 | 0 | 4 | 4 |
| 8 | 1 tube | 0 | 0 | 6 | 6 |

TABLE 7—*Pancreatic (Bassler) Test of Fresh Specimens of Human Urine (None Containing Sugar or Albumin)*

| Case | Estimated with No Incubation | | Incubation, 30 Minutes, Read After Standing 20 Minutes | Incubation, 60 Minutes, Read After Standing 20 Minutes |
|------|------------------------------|--------------------------------------|--|--|
| | Read Imme- diately | Read After Standing 20 Minutes | | |
| 1 | 2 | 4 | 4 | 4 |
| 2 | 0 | 2 | 2 | 2 |
| 3 | 0 | 2 | 2 | 2 |
| 4 | 2 | 2 | 2 | 2 |
| 5 | 2 | 4 | 4 | 4 |
| 6 | 2 | 2 | 2 | 2 |
| 7 | 0 | 2 | 2 | 2 |
| 8 | 2 | 4 | 4 | 4 |

solution admixture has not been considered, have raised the question whether pancreatic juice is obtained The many tests that have been made, especially the usual chemical and laboratory methods for proving the presence of maltose or dextrose, have proved that, according to the presence and the amount of amylopsin existing in the specimen, sugar is promptly formed when it is added to the starch A point of much interest in this connection is that unless amylopsin or some other type of diastatic ferment is present, irrespective of what type or how many iodine-combining factors are also present, the ferment is essential for the formation of sugars This fact is the basis of a new method of estimating the enzyme, which up to the present has not proved satisfactory The saccharogenic methods and Martin's recent article will be discussed later

Two important matters have engaged my attention for the past three years. They are so revolutionary and contradictory to what has been taught and believed that they suggest reinvestigation and revision not only of the starch-iodine tests, but of the whole subject of diastatic enzymes as well.

DIASTATIC ENZYMES IN THE BODY AND THEIR ESTIMATION

Diastatic Enzymes in the Body—The starch and iodine test has been employed from the beginning of my experiments and observations. Since the test of detecting iodine by starch and its reverse purpose was discovered by Conlin and Gaultier de Clambry, and the technic of this quantitative test against enzymes by Wohlgemuth, innumerable analyses of body fluids have been made by them, because of the conversion of starch, they believed that diastatic ferments were present and were the cause of the change. So far as I can learn, consideration was not given to other substances in the fluid that would combine with iodine before the starch (the dextrins and sugars), to the presence of iodine-combining factors of organic nature which would have to be saturated before a blue color would result or to the automatic change that occurs in a boiled starch solution, these considerations, would, of course, seriously interfere with definite conclusions. In the light of my observations too much was taken for granted in all this work, therefore it will have to be done again more accurately.

Of all the factors liable to cause error in the starch-iodine test, especially when it is employed to test for the presence of a diastatic enzyme, the most important one is the greater affinity of dextrins and sugars for iodine as compared to that of starch, and the contained organic substances which also become saturated before starch does.

ESTIMATION OF DIASTATIC ENZYMES

The three great enzymes are the proteolytic, diastatic and lipolytic. While there are phenomena that suggest the presence of a so-called lipase, the presence of such an enzyme has never been proved, nor has it ever been isolated. In a recent article⁴ it was shown that all the changes from neutral oil to the production of fatty acids can be accomplished by weak alkalis alone. As with rennin, the assumption of its existence is not justifiable, and it is possible that a true lipolytic enzyme does not exist. All proteolytic enzymes are dual in their action of conversion. This is true of the one in the stomach as well as of that in the pancreatic juice, both of which require outside activation, that of the stomach from the hydrochloric acid and that of the pancreas from a product of the duodenal mucosa (enterokinase).

4 Bassler, A., and Lutz, J. R. Am J M Sc 168 869 (Dec) 1924

The action of all proteolytic enzymes, however, is slow, perhaps because their function is to break down a most complex substance found in native proteins. My experiments to increase the speed of this action proved that it depends on the incubation as well as on the length of time. As a general rule, this is not true of the diastatic ferments and in my work on diastatic activity with specimens from human beings and from animals, I found that in their action diastatic ferments closely correspond to a catalyzer, the action requires no time, incubation is almost unnecessary, and it occurs at any reasonable temperature, even one that is considerably lower than that of the body. If one prepares tube 1 in the original test (namely, adding 1 cc of duodenal return to 4 cc of the starch solution), shakes it at once and tests for sugar with Benedict's or Fehling's

TABLE 8—*Tests of Duodenal Returns (Containing Pancreatic Juice) Showing Immediate Production of Sugar, and Comparisons of Figures Obtained Immediately and After Incubation*

| Case | 1 Cc Duodenal Return, 4 Cc, 0.5% Starch Solution, Sugar Present | Immediate Units, No Incubation | | Incubation, 30 Minutes, Read After Standing 20 Minutes | Incubation, 60 Minutes, Read After Standing 20 Minutes |
|------|---|--------------------------------|--------------------------------------|--|--|
| | | Read Imme- diately | Read After Standing 20 Minutes | | |
| 1 | + | 10 | 20 | 20 | 20 |
| 2 | + | 12 | 20 | 20 | 20 |
| 3 | + | 6 | 10 | 16 | 20 |
| 4 | Slight trace | 0 | 0 | 4 | 4 |
| 5 | + | 10 | 16 | 20 | 20 |
| 6 | + | 14 | 20 | 20 | 20 |
| 7 | Trace | 2 | 8 | 8 | 10 |
| 8 | + | 4 | 10 | 20 | 20 |
| 9 | + | 2 | 8 | 14 | 16 |
| 10 | ++ | 14 | 20 | 20 | 20 |

solution, the sugar reaction will somewhat depend on the amount of diastatic ferment present, the test, however, is not accurate. Incubation for considerable periods of time does not cause a much greater reaction. All that is necessary is to allow the mixture to stand for a minute or two at room temperature, and definite conversion will occur.

The points made in the foregoing paragraphs evidently were not taken into consideration when a separate estimation of the iodine-combining factors was devised, and prove that there should not be modification of the original test unless some other than the starch-iodine method is found. The test as advanced is not offered as a perfect procedure, but compared to the other methods so far devised for the purpose, it is clinically the best one at present. Even with its possibility for errors, it has served in many instances both as an aid to diagnosis and as a source of suggestions for treatment. Like all laboratory methods, it no doubt is of most value when it is positive. It is a quick, inexpensive and fairly good means of estimating the activity of the pancreas, it is often of value in diabetes mellitus and in pathologic changes in the gallbladder as the concluding lists will show. Finally, as Dolley⁵ has also suggested

⁵ Dolley Am J Anat 35:153 (May) 1925

in his observations, there is no basis for the belief that there is unequal secretion of the enzymes, since histologically all the cells are similar, they go through the same stages of rest and activity. Methods by which all of the enzyme activities are estimated separately fail through their own errors and are unnecessary and time consuming, generally, their use is to be discouraged. I believe that all that is necessary in order to judge the activity of the pancreas is to make estimations of the amylase.

PROGRESS MADE SINCE TEST WAS SUGGESTED

Mellanby⁶ conducted an extensive series of experiments on the mechanism of the external pancreatic secretion. He showed that the entrance of hydrochloric acid into the duodenum does not constitute the essential stimulus for pancreatic secretion as was the belief of Popielski,⁷ but that if an extract of the pyloric mucous membrane is added, a copious secretion occurs. By analyzing this action, he seemed to prove conclusively that the effect was due to the introduction of bile into the duodenum, the acid extract of the pyloric mucous membrane caused this bile to flow and to produce an adequate reaction. The essential factor was the cholic acid contained in the bile salts, since the injection into the duodenum of pure sodium cholate which reacted adequately led to a large secretion of pancreatic juice. He also proved that mucin delays the absorption of bile salts, prevents its hemolysis of the red blood cells and prolongs the action on the pancreas. An important point discovered is that the injection of acidulated bile into the duodenum does not always cause an active pancreatic secretion, and further, that the state of alimentary activity exercises a great influence on the capacity of any given bile to evoke a pancreatic secretion. In a cat recently fed (within four hours) there was a large secretion of pancreatic juice after the injection of slightly acidified (p_H 6.5) bile into the duodenum. If however the cat had not been fed for twenty-four hours, the effective pancreatic stimulant would have been an injection of alkaline (p_H 8) bile into the duodenum.

Accepting Bayliss and Starling's⁸ conclusions it is Mellanby's contention that secretin is important for pancreatic activity. This author shows that cholic acid is operative only in the duodenum, that its absorption is prompt, and that with its resorption the secretin passes into the blood and from thence to the pancreas, and that the immediate pancreatic stimulus is secretin carried to the pancreas by the cholic acid. In their passage through the intestinal mucosa the bile salts absorb the secretin

6 Mellanby, J. *Lancet* 2:215 (July 31) 1926.

7 Popielski. *Arch f d ges Physiol*, 1901.

8 Bayliss and Starling. *J Physiol* 28:325, 1902.

contained in the cells of the mucosa and carry it into the blood and by this means to the pancreas. In this neither the vagus nor the sympathetic nerves are operative, and the secretin in the blood is the only important factor.

Experimenting along these lines with human beings, I found that bile from man diluted five times with 1.5 per cent solution of sodium bicarbonate produced an active flow of pancreatic juice in fifteen minutes. At first I believed that the introduction of bile into the empty stomach would be irritating and perhaps cause vomiting, especially if there was acid in the stomach, this can easily be considered nonexistent, because the empty stomach (even in health) often contains bile regurgitated from the duodenum. It, therefore, was not proved to be true. If residual acid is present, the acid precipitates the bile salts and prevents absorption until it is neutralized again in the duodenum. Lecithin (which is difficult to get into solution) injected directly into the duodenum is destroyed and not absorbed in the blood. As specimens of fresh bile from human beings are difficult to obtain and to keep fresh, one dislikes to employ them because of the danger of carrying infection, and since ox bile is intensely irritating to the alimentary canal of man, the commercial salts of bile was employed. In a mixture of the glycocholate and taurocholate, the commercial salts proved to be as efficient as bile from human beings and pure sodium cholate solution. As none of the constituents of bile seems to have any iodine-combining powers, it was deemed best to use an artificial bile (in which the lecithin was omitted) the formula of which is presented in the list of artificial bile (table 3). The results thus far prove that this is a poor clinical means for stimulating the pancreas, only indifferent specimens for testing being obtained in from five to fifteen minutes after its introduction into the duodenum.

The next phase of this subject seems confusing but really is not. Mellanby has shown that bile itself is the natural stimulant for pancreatic secretion. Solutions of peptone are most active in stimulating the flow of bile, almost as active as solutions of magnesium sulphate. In early work with magnesium sulphate and solutions of peptone the comparison showed that solution of peptone was a better stimulant to employ so far as the pancreas was concerned, magnesium sulphate being more valuable for the biliary system. In many instances when solutions of magnesium sulphate were employed, and even when the flow of bile was active, the unit figures were low, in other instances, they were irregular. It is possible that even when an active flow of bile is produced by magnesium sulphate, the salt will in some way inhibit pancreatic secretion in the short time that it takes to obtain a suitable specimen. I agree with Martin⁹ that when peptone solution is employed,

⁹ Martin, L. Biliary, Pancreatic and Duodenal Studies **39** 343 (March) 1927

the A fraction may be rather uniformly employed in the test, and when magnesium sulphate is used, the B fraction may be more uniformly potent in pancreatic juice. If there is any fear that peptone admixture may be a confusing factor when irregularity of pancreatic flow is caused by the use of magnesium sulphate, properly bicarbonated artificial bile may be employed especially since the salts of bile have no iodine-combining powers.

In a recent article by Martin, the saccharogenic method is preferred to the amylolytic method for estimating the diastatic enzyme of the pancreas. In the early days of my work, sugar was added to the starch solution employed and a quantitative estimation by Benedict's solution was made after the solution used had been incubated and shaken three times. I could not secure uniform results with different quantities of duodenal return even when I employed buffer solutions from p_H 6.7 to 7.6, and it made little difference whether I used these in small or large quantities. In the first place, there was an activity of the enzyme with small quantities of duodenal return which in most instances would not be increased with larger quantities, in other instances there was a slight increase, but this had usually disappeared in the third and fourth tubes. In the second place, with all alkaline copper solutions used (such as that of Folin and Wu which Martin employs), the dextrose formed had 100 per cent reducing effect on the copper solution and the maltose formed only about 76 per cent. These two facts introduced a most serious variance, and even when the picric acid method of estimating sugar was employed (as in blood chemistry), this variant could not be controlled in whatever dilution it was used, although a dilution of not more than 1:500 was employed (Martin suggests 1:600). All my early work was done according to saccharogenic methods. These seemingly are more scientific and deal with a definite substance in sugar rather than with one that varies, such as starch conversion through the dextrins. The results, however, were so varying and beyond understanding and control that the amylolytic test became the preferred one and is the one I would recommend. In this connection I am satisfied that Martin is correct in suggesting the employment of the B fraction. If this is deficient, both the A and C should also be estimated before a final conclusion is made. I also agree with Martin that "storage of the gland," which I formerly believed occurred, is more theoretical than actual. I have learned that it often takes longer to stimulate pancreatic secretion, in a few instances the time is as long as from ten to fifteen minutes after the stimulant is introduced. This is the time in which the B fraction is obtained in an ideal performance. There are distinctly three types of pancreatic flow after stimulation: the prompt, the average and the slow. In these the highest contents of

pancreatic juice would roughly correspond to the A, B or C fractions. In my work the three fractions were kept separate. First the A fraction was examined, if this was normal, I did not proceed, but if this was low, I examined the B and C fractions. The figure expressing the units is the highest figure obtained in any one fraction, in the list of cases that follows this was the routine throughout, the fraction used not being mentioned.

CLINICAL EVALUATION OF THE PANCREATIC TEST (ORIGINAL)

For this purpose, four types of more than 100 cases in which the test was performed have been listed. In this group there was one case of sarcoma of the body and of the tail of the pancreas (which gave a 2 unit reading), an instance of pancreatic fistula following an operation for hemorrhagic pancreatitis (which gave a 6 unit reading) and one case of chronic pancreatitis (which did not give any unit reading). The unit readings were so low that they were excluded from the list. In addition to this, determinations of serum bilirubin and cholecystography were performed in groups 2 and 3, it is not essential to report these observations in this connection. The groups are as follows:

GROUP 1 This group included instances of diabetes mellitus, in which condition it is well known that disorder or disease of the pancreas frequently occurs, it was therefore deduced that if a disorder of the islands of Langerhans was affecting the quantity of the internal secretion of the gland, a more or less general disorder of the cells of the whole pancreas might exist. It was assumed that by testing the external secretion of the gland in proved cases of diabetes mellitus, clinical values of its usefulness would be determined. It may be recalled that in many instances patients with diabetes mellitus have disease of the biliary system, especially gallstones, and while none of the patients gave any suggestions of disorders in the biliary tract, the Lyon-Meltzer method of examination was employed as a check so far as this might be valuable and in no sense as a means of examination for the diagnosis of diabetes.

GROUP 2 In a small series of instances of verified biliary disease, all the patients were carefully examined at operation. The object was to note the incidence of unit values in those in whom the head of the pancreas was definitely thickened, stiffened or hardened, a matter which different surgeons variously estimate according to the results of their examination and the personal equation. It is reported that pathologic changes in the gallbladder are found in from 3 to 20 per cent of the patients who have been operated on for disease of the gallbladder. The deficiencies of the pancreatic test for purposes of diagnosis, the inconsistencies between it and the Meltzer-Lyon method of examination, and the extent to which the Meltzer-Lyon method was positive were noted.

GROUP 3 In this group was included a series of clinical cases of disease of the biliary tract, all the patients had digestive symptoms of direct or reflex type and all had localized symptoms of pain under the right costal margin with objective pain or distinct tenderness on physical examination. A careful analytical history was obtained in all cases, and a differential diagnosis was made in order to ascertain that the right kidney and the appendix were not diseased and that there was no pathologic condition in the colon. All of these patients were also studied by means of the roentgen ray and bilirubin tests of the serum were made, unless the symptoms showed conclusively that disease of the biliary tract was present, the cases were not reported in this group. The object was to obtain an average unit reading to compare with that of the group of patients without pathologic changes in the gallbladder, and

TABLE 9—*Pancreatic Unit and Meltzer-Lyon Test in Diabetes (Group 1) **

| Case | Diagnosis | Meltzer-Lyon Test | Pancreatic Units |
|------|-------------------|-------------------|------------------|
| 1 | Diabetes | Positive | 8 |
| 2 | Diabetes (marked) | Negative | 0 |
| 3 | Diabetes | Negative | 4 |
| 4 | Diabetes | Positive | 4 |
| 5 | Diabetes (marked) | Negative | 0 |
| 6 | Diabetes (marked) | Negative | 0 |
| 7 | Diabetes | Positive | 4 |
| 8 | Diabetes (marked) | Negative | 2 |
| 9 | Diabetes (marked) | Negative | 0 |
| 10 | Diabetes | Negative | 6 |
| 11 | Diabetes | Negative | 20 |
| 12 | Diabetes | Negative | 4 |
| 13 | Diabetes | Negative | 20 |
| 14 | Diabetes | Negative | 4 |
| 15 | Diabetes | Negative | 8 |

* The pancreatic units averaged 5½ units (normal average, 10 units), deficiency was present in 86⅔ per cent and absent in 13⅓ per cent, the Meltzer-Lyon test was negative in 80 per cent and positive in 20 per cent.

to note the differences and inconsistencies between this method and the Meltzer-Lyon method of diagnosis, I also wished to ascertain to what extent the Meltzer-Lyon method was positive.

GROUP 4 This group contained a miscellaneous group of patients who did not show any signs of diabetes or disease of the biliary tract, they were carefully examined for these conditions before being included in the group. The object was to obtain an average unit reading which could be compared with the reading of the diabetic patients and of those with clinical types of disease of the biliary tract, it was also to judge the efficacy of the Meltzer-Lyon method of diagnosis in negative cases of disease of the biliary tract.

If a unit reading below 10 is considered positive, it is evident that the majority of patients with diabetes mellitus have a deficiency of the external as well as of the internal (islands of Langerhans) enzyme secretion of the pancreas, in this way the value of the test is manifest. In cases 2, 5, 6 and 9 all readings were negative in pancreatic units, in case 8 marked hypopancreorrhea existed. In these five cases it was

interesting to note that difficulty was experienced in keeping the specimens of urine sugar-free or approximately so when the patients were placed on diets that maintained normal basal metabolism. To accomplish this, it was necessary to give these patients daily doses of insulin in addition to the specified diet. It was possible to reduce the dosage of insulin about the second or third day when pancreatic feedings of from 100 to 250 Gm of pickled gland were given daily. There was also marked general improvement in health, strength and well-being. This was so striking (in these five cases, as well as in four others) that an

TABLE 10—*Pancreatic Units and Meltzer-Lyon Test in Verified Diseases of the Gallbladder (Group 2)**

| Case | Diagnosis | Meltzer-Lyon Test | Pancreatic Units | Operation |
|------|--|-------------------|------------------|--|
| 1 | Chronic cholecystitis | Positive | 4 | Cholecystectomy, stiffened pancreas |
| 2 | Chronic cholangitis | Positive | 12 | Gallbladder removed before tests, normal pancreas |
| 3 | Chronic cholecystitis | Positive | 2 | Cholecystectomy, stiffened pancreas |
| 4 | Chronic cholecystitis (with stones) | Positive | 1 | Cholecystectomy, stiffened pancreas |
| 5 | Chronic cholecystitis (with stones) | Negative | 6 | Cholecystectomy, stiffened pancreas |
| 6 | Chronic cholecystitis (with stones and ulcer) | Negative | 2 | Cholecystectomy, gastro enterostomy, ulcer attached to pancreas which was firm |
| 7 | Chronic cholecystitis (with stones) | Negative | 6 | Cholecystectomy, stiffened pancreas |
| 8 | Chronic cholecystitis (with stones) | Negative | 10 | Cholecystectomy, normal pancreas |
| 9 | Chronic cholecystitis (stones and gastric carcinoma) | Positive | 10 | Cholecystectomy (sclerosed gallbladder) partial gastrectomy, normal pancreas |
| 10 | Chronic cholecystitis (with stones) | Negative | 18 | Cholecystectomy, normal pancreas |
| 11 | Chronic cholangitis | Negative | 0 | Cholecystectomy, stiffened pancreas |
| 12 | Chronic cholecystitis | Positive | 0 | Cholecystectomy, stiffened pancreas |
| 13 | Chronic cholecystitis (steady jaundice) | Positive | 2 | Cholecystectomy, firm pancreas |
| 14 | Chronic cholecystitis (with stones) | Negative | 2-18 | Cholecystectomy, stiffened pancreas |
| 15 | Chronic cholecystitis | Negative | 18 | Cholecystectomy, normal pancreas |

* The average pancreatic units were $6\frac{1}{2}$ (normal low average, 10 units), averaged stiffened pancreas were $2\frac{1}{2}$ units, the pancreas was considered involved in ten of these fifteen cases (about 67 per cent) and not involved in five of these fifteen cases (about 33 per cent), the Lyon-Meltzer test was positive in seven of these fifteen cases (about 45 per cent) and negative in eight of these fifteen cases (about 55 per cent)

explanation was sought, while academic, the following explanation is worthy of consideration. It may be that in diseases and disorders of the pancreas causing the condition of diabetes, the deficiency of the enzyme content of the external secretion in some way brings about a deficient type of end-sugars for resorption, the liver cells cannot store these sugars, therefore they flow into the general blood stream and appear in the urine. These sugars can be oxidized by insulin. If, on the other hand, pancreatic substances are added to the digestion to make up the shortage in the pancreatic juice, the sugars are hydrolyzed in more complete form and are then capable of being stored and oxidized with lesser amounts of insulin. As an argument against this, one must consider that in the feeding of pancreatic gland substances some islands

of Langerhans are ingested, perhaps these cells contain insulin, which, when resorbed, answers the same purpose as insulin administered hypodermically

The main point, however, is the fact that the pancreatic test was accurate as it verified known clinical facts in showing low pancreatic units in the returns. Except in cases 11 and 13, the unit contents were noticeably low or absent, even in the total unit readings, the average was only $5\frac{3}{5}$ units, almost half of the low normal (10 units). As there are types of diabetes in which a normal pancreas is found, and since both of these cases were of simple types and easily controlled by diet alone, they could be excluded from the list, this would then leave the average content of the remainder only $3\frac{5}{13}$ units. Manifestly, the returns from the duodenum in these patients contained all of the iodine-combining factors (with the exception of the enzyme that causes starch conversion in the pancreatic juice), and yet the value of the test was conclusive in the procedure as originally advanced.

There was some doubt concerning the involvement of the pancreas in case 9. The carcinoma was definitely located in the pyloric region, and there was considerable involvement of the glands. Decision on this point was difficult. In case 14 the second unit estimation represents the result of a test made fifteen weeks after operation. It is not uncommon (in the ideal case) for congestion of the head of the pancreas to subside after the gallbladder has been removed, the external secretion (and often the internal) becoming normal again. However, in this small group the average pancreatic unit is almost as low as that for diabetic patients, and the reading for those with definite changes in the pancreas is almost one fifth of the low normal figure. In all of these cases the icterus index was above 7, that of case 13 being 28 (Rosenheim's method employed). In this group, the comparison between the estimation of units and the Meltzer-Lyon method of diagnosis is interesting. The pancreatic unit estimations are not offered as a means for diagnosing disease of the gallbladder, although this test is often valuable in judging whether or not the patient should be operated on¹⁰ rather than treated medically. It is interesting, however, to know that by the unit estimation a higher percentage of clinical value was obtained than by the Meltzer-Lyon method. The results are conclusive as to the clinical value of the test.

In this group it was decided that operation should be performed in cases 9, 14, 20, 26, 30, 31 and 34. In case 9, the patient reported marked improvement after medical treatment, it was not possible to make a second pancreatic test. Case 14 was not traceable, and in case 20 the

¹⁰ Bassler, A., and Lutz, J. R. *M. J. & Record* (supp.) **122** 275 and 321, 1925

operative risk was great, a stone being present in the pelvis of a kidney, the other kidney had been removed because of a stone, and a discharging sinus remained. There was also marked myocarditis. Following simple treatment, the patient had not had pain in the gallbladder up to the time this article was written (a period of fifteen months). In case 26 operation would have been a mistake, as when constant drainage of bile and

TABLE 11—*Pancreatic and Meltzer-Lyon Tests in Clinical Types of Disease of the Biliary Tract (Group 3) **

| Case | Diagnosis | Meltzer-Lyon Test | Pancreatic Units |
|------|-------------------------------------|-------------------|------------------|
| 1 | Chronic cholecystitis | Positive | 6 |
| 2 | Chronic cholecystitis | Positive | 8 |
| 3 | Chronic cholecystitis | Positive | 4-18 |
| 4 | Chronic cholecystitis | Positive | 9 |
| 5 | Chronic cholecystitis | Positive | 6 |
| 6 | Chronic cholecystitis | Positive | 6-12 |
| 7 | Chronic cholecystitis | Positive | 6 |
| 8 | Chronic cholecystitis | Negative | 4 |
| 9 | Chronic cholecystitis | Negative | 4 |
| 10 | Chronic cholecystitis | Positive | 12 |
| 11 | Chronic cholecystitis | Positive | 6-14 |
| 12 | Chronic cholecystitis | Negative | 6 |
| 13 | Chronic cholecystitis | Negative | 6-18 |
| 14 | Chronic cholecystitis | Negative | 2 |
| 15 | Chronic cholecystitis | Negative | 20 |
| 16 | Chronic cholecystitis | Negative | 6-20 |
| 17 | Chronic cholecystitis | Positive | 20 |
| 18 | Chronic cholecystitis | Negative | 14 |
| 19 | Chronic cholecystitis | Negative | 16 |
| 20 | Chronic cholecystitis (with stones) | Positive | 0 |
| 21 | Chronic cholecystitis | Negative | 20 |
| 22 | Chronic cholecystitis | Negative | 6 |
| 23 | Chronic cholecystitis | Positive | 20 |
| 24 | Chronic cholecystitis | Positive | 20 |
| 25 | Chronic cholecystitis | Positive | 16 |
| 26 | Chronic cholecystitis | Negative | 2-18 |
| 27 | Chronic cholecystitis | Positive | 7 |
| 28 | Chronic cholecystitis | Negative | 18 |
| 29 | Chronic cholecystitis | Negative | 4 |
| 30 | Chronic cholecystitis (with stones) | Positive | 20 |
| 31 | Chronic cholecystitis (with stones) | Positive | 20 |
| 32 | Chronic cholecystitis | Positive | 2-12 |
| 33 | Chronic cholecystitis | Negative | 20 |
| 34 | Chronic cholecystitis | Positive | 2 |
| 35 | Chronic cholecystitis | Negative | 10 |
| 36 | Chronic cholecystitis | Positive | 6 |
| 37 | Chronic cholecystitis | Positive | 2-10 |
| 38 | Chronic cholecystitis | Positive | 20 |
| 39 | Chronic cholecystitis | Negative | 8 |
| 40 | Chronic cholecystitis | Positive | 6 |

* The average number of pancreatic units in all was 9½, the unit readings were positive as to the pancreas in twenty-five cases and negative as to pancreas in fifteen cases, the Lyon-Meltzer test was positive as to the gallbladder in twenty-three cases and negative in seventeen cases. When two figures occur in the column giving the units, the first was obtained before and the second after the time of treatment.

treatment were instituted, the patient made a good symptomatic recovery, with restoration of pancreatic function. In cases 30 and 31, the patients were not given any treatment to speak of, they have been comparatively free from symptoms and therefore have refused operation. In case 34, the patient had an extensive pulmonary tuberculosis, and the value of an operation was questionable.

The average unit readings of the whole group was $9\frac{3}{4}$, fifteen cases in which the units were normal or above and twelve in which they were of the highest range possible were included in this group. The test in 62.5 per cent of this group showed that diseases of the gallbladder existed which affected the pancreas, it showed that only 37.5 per cent were free from these conditions. In the cases Deaver reported, the pancreas was involved in 46 per cent of the instances of disease of the gallbladder, and in practically one half of the cases glycosuria was present before operation. These figures for the pancreatic test are strongly suggestive of the fact that in diseases of the gallbladder functional disturbances of the pancreas represent a much higher incidence than this, and that some of the congestive or hyaline types of pathologic conditions of the acini are not palpable at operation. It is well known that glycosuria as a symptom of pancreatic disease is not a dependable clinical symptom, because most often it does not exist in general disease of the gland, if it does, it is usually transient. It is interesting to note in this group that the unit figures are even more valuable clinically in this indirect means of estimating pathologic changes in the gallbladder than in the more direct means of the Meltzer-Lyon method. The inconsistencies between the two in individual cases are not sufficient for me to make any deduction from, especially as disease of the biliary system may exist without pancreatic involvement or change in function. It seems certain, however, that in disease of the biliary tract the pancreas should be examined for additional information, especially in helping to decide which patient should be operated on and which should receive medical treatment. Improvement has been noted in a considerable number of cases of chronic cholecystitis in which the patients have received treatment, especially in cases in which the patients did not have gallstones.

Case 4 was interesting in that there was a transient glycosuria, with a blood sugar averaging 0.17 per cent on three occasions. This was an instance of potential diabetes, although when the patient ate the average kind and amount of food the specimens of urine were more often negative than positive when tested for sugar, and when positive, the quantity of sugar was always below 0.5 per cent. In case 5, numerous Welch bacilli were found and the feces were gram-positive when the patient was eating a normal test diet (saccharobutyric toxemia). This type of intestinal infection usually causes the blood sugar to become higher than normal; this is sometimes true also of the icterus index. In this patient, both were above normal. Case 11 is excluded because the general health and weight of the patient improved, and the pancreatic units, which were not much below normal in the first instance, soon increased. In case 13, it is possible that the pancreas was involved; operation was not performed. In case 26 the patient was operated on, a great many adhesions were present, which originated in the first part of the duodenum spread

in all directions The head of the pancreas was felt with great difficulty, and it was impossible to state whether or not it was firmer than normal The slight lowering in the pancreatic units in case 33 is not accounted for, and I cannot offer any suggestions, case 35 was probably an instance of chronic cholecystitis, but there were not enough clinical symptoms to warrant this diagnosis A marked chronic gastritis existed, with a

TABLE 12—*Pancreatic and Meltzer-Lyon Tests in Nonbiliary Tract Disease (Group 4)*

| Case | Diagnosis | Meltzer Lyon Test | Pancreatic Units |
|------|---|-------------------|------------------|
| 1 | Migraine | Negative | 14 |
| 2 | Redundant colon, stasis, chronic constipation | Negative | 12 |
| 3 | Arthritis | Negative | 20 |
| 4 | Hypopituitarism, hyperglycemia | Negative | 4 |
| 5 | Saccharobutyric toxemia, chronic diarrhea | Negative | 4 |
| 6 | Infected tonsils, chronic gastritis | Negative | 10 |
| 7 | Colonic stasis, menopause | Positive | 15 |
| 8 | Saccharobutyric toxemia | Negative | 20 |
| 9 | Ptosis | Negative | 20 |
| 10 | Colitis, ptosis | Negative | 18 |
| 11 | Ptosis, debility | Positive | 8-20 |
| 12 | Gastric ulcer | Negative | 14 |
| 13 | Gastric cancer | Positive | 6 |
| 14 | Cardiospasm | Positive | 20 |
| 15 | Neuritis, toxemia, indol type | Negative | 8 |
| 16 | Colitis | Negative | 20 |
| 17 | Subacute appendicitis | Negative | 20 |
| 18 | Colitis, toxemia, indol type | Negative | 18 |
| 19 | Toxemia, indol type | Negative | 18 |
| 20 | Ptosis, toxemia, indol type | Negative | 20 |
| 21 | Arteriosclerosis, nephritis | Negative | 20 |
| 22 | Toxemia, indol type | Negative | 20 |
| 23 | Hart's biliary cirrhosis | Positive | 20 |
| 24 | Ptosis | Negative | 20 |
| 25 | Ileocolonic stasis | Negative | 10 |
| 26 | Duodenal ulcer | Negative | 4 |
| 27 | Toxemia, indol type | Negative | 10 |
| 28 | Toxemia, indol type | Negative | 20 |
| 29 | Menopause | Negative | 20 |
| 30 | Saccharobutyric toxemia, colonic stasis | Negative | 20 |
| 31 | Saccharobutyric toxemia | Negative | 20 |
| 32 | Psychoneurosis | Negative | 20 |
| 33 | Colonic stasis, epilepsy, debility | Negative | 8 |
| 34 | Ptosis, colonic stasis, uterine fibrosis | Negative | 14 |
| 35 | Chronic gastritis, chronic cholecystitis (?) | Positive | 8 |
| 36 | Ileocolonic stasis, toxemia, indol type | Negative | 14 |
| 37 | Gastroduodenitis | Negative | 20 |
| 38 | Chronic gastritis | Negative | 20 |
| 39 | Chronic appendicitis, colonic stasis | Negative | 20 |
| 40 | Hemorrhagic gastritis, ptosis | Negative | 16 |

* In all cases the average pancreatic units were 15+, below normal in seven cases (except case 7) and above normal in thirty-three cases (except case 7), the Meltzer-Lyon test was positive in six cases and negative in thirty-four cases

history of three attacks of catarrhal jaundice which had extended over a period of seven years Even with these more or less doubtful cases considered in the reckoning, the pancreatic units were 15 plus (the normal range being between 8 and 14, or 10 taken as the low normal), and twenty-nine cases were above 14 in unit reading In these cases of disease of the gallbladder in which the pancreatic unit test was negative (omitting cases 4 and 35 in the calculation), the Meltzer-Lyon test was positive in 4 or 10 per cent

These figures of pancreatic units when compared with lists numbers 1, 2 and 3, strongly suggest the clinical value of estimating pancreatic efficiency in diabetes and in diseases of the gallbladder and of the pancreas, as well as the value of the original test. Inconsistencies which are not explainable will be encountered, but when clinical diagnoses of diabetes and of disease of the gallbladder and of the pancreas can be made, this test adds information that is often of signal service when it is positive.

CONCLUSIONS

A technic is described to obviate the possibility of peptone admixture in the specimen.

The Piersol, Bockus and Shay modifications to estimate the iodine-combining factors other than those that occur as a result of the action of the enzyme on starch solutions are of no practical value and nullify the original test.

Sugars, dextrans and animal substances in solution have a greater combining power for iodine than has starch when present in the same solution, and it is not until these have been saturated that the characteristic blue color of the iodide of starch is seen.

Boiled starch is not a stable solution and hydrolyzes considerably after cooling. This is accomplished by simple chemical change and also by the action of an enzyme contained in the encasement of the starch granule. In the performance of the original test, this need not be accounted for. To estimate this, as well as all of the iodine-combining factors contained in body fluids, a procedure would have to be devised with this test which would not permit an addition of iodine greater than 1 minim (0.06 cc) of the twenty-fifth normal solution suggested in the original test.

Constituents of bile in solution, singly or in combination, have no conversion power on starch, nor do they contain iodine-combining factors. Natural bile from animals is heavy in combining factors, the same being true of blood serum, feces and urine of human beings. The latter fact has not been taken into consideration in tests for diastatic enzymes in the past, and thus the presence and amounts of such enzymes have been too much taken for granted.

Pancreatic juice is present in duodenal returns and does not mix with bile while it is in the biliary tract.

The action of amylopsin is that of a catalyzer, and incubation, time and heating to body temperature are usually not necessary. The end-products of its action on boiled starch are sugars, mostly maltose, and considerable dextrose.

Dissociation of the pancreatic enzymes does not occur in disorders and diseases of the gland. If amylopsin is deficient, there will also be a lack of trypsin.

As is true of rennin in the stomach, there is much doubt that a ferment called lipase exists in pancreatic juice

Mellanby's physiologic observations on bile salts, a stimulant that causes a flow of pancreatic juice, are confirmed. As artificial bile has no iodine-combining power, it may be employed as a poor substitute for peptone (and also magnesium sulphate) for specimens of pancreatic juice. With the proper technic, however, peptone solution is the most satisfactory and can also be used for specimens of bile. For the pancreas, magnesium sulphate is often too variable for testing purposes.

In making the test, employ bile fraction A. If this is low, test fraction B and if this is low, fraction C. The efficiency of the pancreas is expressed in the one that gives the highest number of units.

The amylolytic is superior to the saccharogenic testing methods for clinical work. It is simpler and far more accurate.

The original test is of value in diabetes mellitus, both in diagnostic and therapeutic ways. It helps in the understanding of true pancreatic disease. A digestive reason for diabetes is presented, and when the test is definite, it shows when pancreatic feedings should be employed, the dosage of insulin may then perhaps be reduced or discontinued.

A series of instances of verified diseases of the gallbladder is presented in which the test was of diagnostic value and helpful in differentiating the operative from the medical type of case, a matter of no small moment in chronic cholecystitis.

A series of clinical types of disorders of the gallbladder is presented in which the test was of value. These, with the foregoing and the subsequent group, show the relative value of testing the pancreas. They also suggest the limited value of the Meltzer-Lyon method in diagnosing these disorders.

I believe that it is advisable to employ this test in clinical work and in the way it was originally proposed. Unlike most laboratory tests that are of value only when positive, it also has a value when negative. It has been a distinct help in my work, and on not a few occasions has it cleared up a doubt or given a suggestion that was well worth while.

DISCUSSION

DR HARRY SHAY, Philadelphia. The disparity between the physiologic importance and the low level of clinical information regarding the pancreas is so marked that any test accurately determining its functional activity is of value. However, any clinical functional test must satisfy at least three postulates: (1) accuracy, (2) simplicity of technic and (3) test function only of organ concerned. I do not question the accuracy of the author's work, I do not doubt the simplicity of the test, but I should like to question its integrity in testing only the function of the pancreas. There is no doubt that dilution factors from sources other than the pancreas must be considered, and it cannot be denied that these dilution factors must vary at different times. More important, however, is the question whether the enzyme which is being tested for originates solely in the

pancreas As early as 1876, Grutzner showed that extracts of duodenal gland substance from various animals showed evidence of a diastatic ferment This was confirmed by Mendeldorf and Glaesner, and, in 1924, by Bergman, Dukes and Yarlborough Using the method of preparation of the last named investigators, I found evidence of a diastatic ferment in the extracts from the mucosa and submucosa of the duodenum shortly after the death of a patient It, therefore, seems improbable that a pancreatic test based on the diastatic ferment as obtained through the duodenal tube can be of great value

Dr Bassler indicated that there was no necessity for the modification I suggested I did not hear any mention of the absorption factor of peptone or duodenal fluid While it is true that the bile salts did not show any absorption factors, bile, itself, did I would like to know how Dr Bassler accounts for this absorption in the reaction involved in the test for the amylolytic ferment As strong a case can be made against the value of a pancreatic test based on the determination of pancreatic lipase While the presence of a gastric lipase is not settled, many physiologists agree that there is such an enzyme The addition of gastric secretion to the duodenal contents occurs at many stages in the collection of duodenal material for examination According to Starling, gastric amylolysis is greatest at the beginning of gastric digestion when concentration of hydrochloric acid has not reached a high degree Is it not possible, therefore, that the activity of gastric lipase may be enhanced when it gets into the duodenum, a factor which cannot be ruled out in any of the pancreatic tests based on determination of lipase? Of the three enzymes, it remains for trypsin to supply the bases for a pancreatic test which is dependent on determination of enzyme My colleagues and I are at work on such a test, but, unfortunately, we have not had sufficient experience with it to make any report

DR FRANK SMITHIES, Chicago It is questionable whether the function of the pancreas can be judged by the estimation of one ferment I am not saying this without experience Physiologists who have worked with pancreatic fistulas or direct catheterization of the duets have shown that the several ferments may vary at different times, under different stimuli and during different periods of the ordinary daily cycle, and that variations occur not only with respect to total output, but in the qualitative factor But if one happens to be so excellent a clinician as Dr Bassler is, I have no doubt that the results obtained by the estimation of one ferment are a certain guide in the diagnosis of disease Personally, I should not be satisfied with his test, as a test to be depended on A few years ago, using the Gross-Fuld-Wohlgemuth method, I performed many hundreds of tests to estimate pancreatic ferments In practically all instances, I could demonstrate amylase in "normal" quantity, whereas other ferments were often lacking It happened that at that time the "discovery" of a peptid-splitting "enzyme" in saliva was announced I investigated this at the time that I was working on pancreatic ferments Finally, I showed that if the extracts were sterilized before the ferment test was applied, practically all of these so-called "ferments" disappeared The whole picture of this constant amylolytic activity supposedly due to the pancreas could be mimicked by inoculating sterile extracts with the organisms common to the mouth, throat and stomach Hence, it would appear that much of the amylolytic "ferment" activity of the pancreas is due to nothing more than ordinary starch conversion by bacteria present in nonsterile extracts

DR ANTHONY BASSLER, New York I did not offer this test as an accurate one, and I make no such claims for it today, yet as the years have gone by my co-workers and I have become more convinced that the test has clinical value.

Accuracy in this field of work is difficult. When one thinks of all that happens, the stimulation of the biliary system, the gallbladder, the liver, the pancreas and the associated phenomena that occur in the initiation of digestion, one can see how difficult it is to come to any definite conclusion. I have grave doubts about the possibility of a dye method being devised to test the efficiency of the pancreas. I should be delighted to have it occur, but it looks impossible to me. We did not work on the absorption factors of peptone and duodenal juice. We figured that the average peptone output of the stomach is approximately 5 per cent. We simply estimated against that in the beginning of the work. As we have never been able to acquire a specimen of duodenal juice, except from animals at autopsy and in extracts, we do not know what that factor is. If one mixes neutral fat with a weak solution of sodium carbonate, which is the salt in pancreatic juice, one can see, with the microscope, every phenomena of fat digestion that is known. I have grave doubts that a ferment known as lipase or that the so-called rennin in the stomach really exists. Formerly, in 100 cholecystectomies performed for chronic cholecystitis there were 51 per cent of recurrences. We came to the conclusion that we were not selecting operative material wisely enough when selection was based on the intensity of the symptoms and the length of history. We then resorted to this method. If I were a patient with chronic cholecystitis and if I felt miserable from it, I would want somebody to test my pancreas in this way. I question very much whether I would permit myself to be operated on unless the output of the pancreas was low. If the output is low and we know that there is a cholecystitis, one can advise operation. Since we have adopted that policy, there have been only four recurrences in about sixty in which cholecystectomy was performed. This was accomplished on the basis of the test alone.

PERITONITIS

III ACTIVE IMMUNIZATION AGAINST EXPERIMENTAL B COLI PERITONITIS ~

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AND

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In a previous communication,¹ the difficulties involved in the production of peritonitis and especially of fatal peritonitis were pointed out. It was found ² that in dogs the intraperitoneal injection of virulent colon bacilli suspended in gum tragacanth always produced peritonitis which was invariably fatal. The purpose of this investigation was to determine the possibility of inducing active immunity against this type of fatal peritonitis.

EXPERIMENTAL WORK

Immunization with B Coli Communis by the Peritoneal Route—Twelve dogs were injected intraperitoneally with twenty-four hour cultures of *Bacillus coli-communis* 300³ in 0.9 per cent sodium chloride. In all these experiments *B coli-communis* 300³ was used. Four injections were given, the intervals between successive ones being three days. The initial dose consisted of the saline washings of one agar slant, and the remaining three doses of two, three and four agar slants, respectively.

Nine of the twelve animals were injected with living and three with killed bacteria. Seven of the nine injected with living bacteria received a peritonitis-producing intraperitoneal injection of *B coli* in gum tragacanth ten days after the last immunizing dose. The remaining two animals were injected with the bacteria in gum tragacanth four months after the last immunizing dose. The peritonitis-producing dose consisted of three agar slants of *B coli* 300 in 40 cc. of a 2.5 per cent suspension of gum tragacanth in 0.9 per cent sodium chloride. The nine animals survived.

The three dogs which received immunizing doses of killed bacteria (by heating for one hour at 56 C) were given the peritonitis-producing intraperitoneal injection fourteen days after the last immunizing dose. The three animals survived.

* From the Department of Pathology, Western Reserve University School of Medicine

* Aided by a grant from the American Medical Association

1 Steinberg, B. Am J Path 2 415, 1926

2 Steinberg, B. J Exper Med 42 83, 1925. Steinberg, B., and Goldblatt, H. Studies on Peritonitis, Arch Int Med 39 446 (March) 1927

3 Steinberg, B., and Ecker, E. E. J Exper Med 43 443, 1926

Six nonimmunized control dogs that received similar peritonitis-producing doses of *B coli* in gum tragacanth succumbed in less than twenty-four hours. Autopsy of these animals showed severe hemorrhagic serofibrinous peritonitis.

Two additional dogs were immunized by the peritoneal route. Ten days after the last immunizing dose, one animal was given intravenously one-quarter slant and the other one slant of living *B coli* 300 in 5 cc of 0.9 per cent sodium chloride. Both animals survived.

Of two nonimmunized control dogs, one received intravenously one-quarter slant of living and the other one-quarter slant of killed *B coli* 300 in 5 cc of 0.9 per cent sodium chloride. Both dogs died. The control animal injected with living bacteria died in three days, and at autopsy showed many abscesses in the myocardium of both ventricles. Smears and cultures of the abscesses showed *B coli*. The dog injected with killed organisms died in twenty-four hours, and autopsy revealed only severe cloudy swelling of the kidneys, liver and myocardium.

Immunization with B. Coli by the Subcutaneous Route—Three dogs received subcutaneous immunizing doses of living *B coli* in saline solution in similar quantities and at the same intervals as did the dogs that were immunized by intraperitoneal injections. Two of these animals were given the peritonitis-producing intraperitoneal injection ten days, and one, thirty days, after the last immunizing dose. The three animals survived.

Three nonimmunized control dogs died in less than twenty-four hours following the peritonitis-producing dose. Autopsy showed hemorrhagic serofibrinous peritonitis.

Immunization with Staphylococcus Albus by the Peritoneal Route—Three dogs were given intraperitoneal injections of twenty-four hour cultures of *Staphylococcus albus* in 0.9 per cent sodium chloride. Four injections were given three days apart. The initial dose consisted of the saline washings of one agar slant, and the remaining three doses, of two, three and four agar slants, respectively. Ten days after the last injection of staphylococcus the dogs were given intraperitoneal injections of a peritonitis-producing dose of *B coli* 300 suspended in gum tragacanth. The three animals died in less than twenty-four hours. Autopsies revealed the usual hemorrhagic serofibrinous peritonitis.

SUMMARY AND CONCLUSIONS

Active immunity which lasts at least four months can be produced in dogs against fatal *B coli* peritonitis.

This immunity can be induced by the subcutaneous as well as by the peritoneal route.

Because the subcutaneous route is effective, and because the peritoneal route also protects against a lethal intravenous injection of *B coli*, the immunity induced is considered to be of a general nature, at least in part.

Immunization with staphylococci did not protect against fatal *B coli* peritonitis.

BLOOD VOLUME IN EDEMA OF GLOMERULAR NEPHRITIS AND NEPHROSIS^{*}

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AND

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The pathogenesis of edema of renal origin is concerned with changes in the blood, vessels and tissues. A review of the literature on the subject is confusing and unsatisfactory. Bright asserted that the depletion of albumin in the blood changed the physicochemical balance and edema resulted. Later Senator suggested the vascular element, and in recent years Fischer has implicated the tissue cells in the genesis of edema. The part played by the blood has interested many observers, but the exact significance of its volume in this connection has not been clear. The following brief excerpts from Loeb's¹ review of the subject of edema depict the prevailing confusion.

Volhard² stated that in acute glomerular nephritis with edema there is no dilution of the blood, while without edema there may be dilution. In the latter, because of the renal block, water is retained in the blood, in the former water and salts are retained in the tissues. He also asserted that in anuria without edema there is dilution of the blood. Volhard interpreted dilution of the blood, or, as he designates it "polyemia," as not constantly followed by edema of the tissues, but caused by renal insufficiency and retention of water in the blood. Reiss³ stated that in edematous cases there is hydremia, this term, according to his usage, implies increased volume of blood (hydremic plethora or polyemia). Nonnenbruch⁴ did not find constant relationship between renal edema and polyemia (increased volume of blood). Loeb believed that transitory polyemia and hydremia may precede edema of the tissues, and that when diuresis occurs, a similar transitory condition will take place. Loeb stated that it is assumed that plethoric conditions of the blood occur in acute glomerular nephritis and that a hydremic plethora also occurs in

^{*} From the Division of Medicine of the Mayo Clinic and the Mayo Foundation.

1 Loeb, Leo. Edema, *Medicine* 2: 171, 1923.

2 Volhard, Franz and Fahr, K. T. *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914.

3 Reiss, quoted by Loeb (footnote 1).

4 Nonnenbruch, W. Ueber extrarenale Odemgenese und Vorkommen von konzentriertem Blut bei hydropischen Nierenkranken, *Deutsches Arch. f. klin. Med.* 136: 170, 1921.

cardiac edema Frey⁵ observed this increase in nephrosis, Widal⁶ observed it in chronic nephritis which preceded or accompanied the edema. Loeb criticized the methods on which the foregoing conclusions were based. Widal used the refractometric method, and with low values for the serum proteins, assumed the existence of polyemia (increased volume of blood due to fluids). Likewise fluctuations or changes in the percentage of hemoglobin and erythrocytes have been assumed to be due to dilution phenomena.

The data in the literature relative to changes in the volume of the blood are largely valueless because of the lack of a method for determining the volume of blood and of plasma. Changes in volume have been estimated on the basis of percentage of changes in single constituents. Percentage changes in the serum proteins do not necessarily indicate changes in the absolute volume of the blood or plasma. Similarly, variations in the percentage of hemoglobin and erythrocytes may reflect absolute and not percentage decreases. Conclusions with regard to the status of the volume of blood and of plasma in disease were impossible until a clinical method for its determination was forthcoming.

NOMENCLATURE⁷

The following terms for different volumes of blood have been suggested: "normovolemia" for a normal volume, "hypervolemia" for an

5 Frey, quoted by Loeb (footnote 1)

6 Widal, F. Die Kochsalzentziehungskur in der Brightischen Nierenkrankheit, Differenzierung der Chloruraemie und der Azotaemie, Verhandl. d. Kongress Med. 26 43, 1909

7 On etymologic grounds, objections have been raised to the proposed terms. The first objection is to the hybrid derivations of the Greek and Latin words. Current usage has led to the acceptance of words of like derivation, such as hypertension and volumetric. Objection has also been raised to the use of the derivative "vol" rather than "volum," but the use of the entire root creates a word lacking euphony, and so the shorter form has been used. The third objection has been directed against the policy of coining additional words. To state one man's opinion, "Why clutter up our already overburdened vocabulary?" This attitude is not justifiable when available terms are not at hand. There are no terms to indicate decreased volume of blood, while those in usage to designate increased volume are ambiguous and not descriptive. Hydremia, according to Dorland's dictionary, is "A condition in which there is an excess of the fluid portion of the blood." This does not implicate an increase in the total volume, as the fluid may be increased with a small volume of blood. It would be necessary to state that the increase was absolute and not percentile. Polyemia, according to this authority, is "plethora," or an "increase in the volume of blood." The increase may be due to either cells or fluid, or both. "Hydremic plethora," according to current usage, would indicate a large volume of blood, due chiefly to the increase in fluid. Anhydremia is a "deficiency in the fluid portion of the blood." No volume status is implicated in this definition, as the volume may be

(Footnote continued on following page)

increased volume and "hypovolemia" for a decreased volume. The three major states of volume, normal, increased and decreased, are subject alike to three possible variations, depending on the ratio as cells to plasma or cell volume to plasma volume and are designated as "simple," "oligocythemmic" and "polycythemic." Chart 1 shows the nine theoretical variations in the volumes of blood and of plasma and their corresponding clinical states.

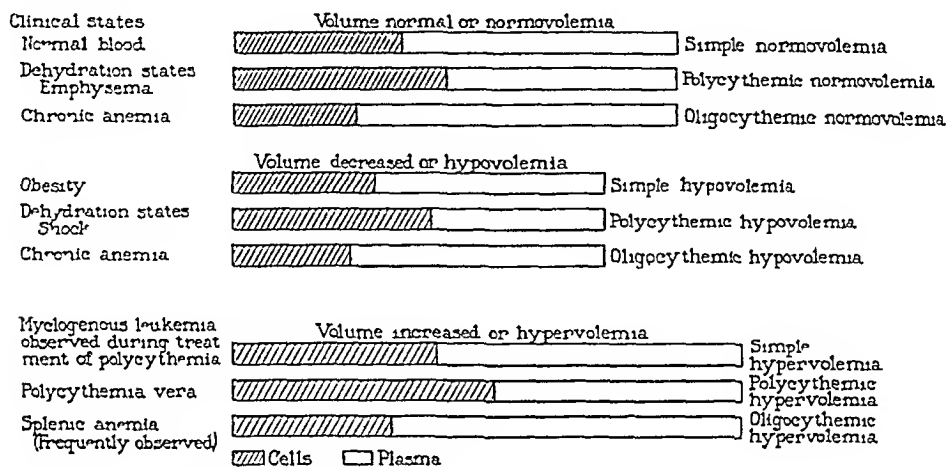


Chart 1—Diagrammatic representation of possible states of the volume of blood, according to body weight, with different cell to plasma relationships

METHOD

In recent years, two methods have been described for the clinical determination of the volume of blood, the carbon monoxide and the dye. The dye method of Keith, Rowntree and Geraghty,⁸ has proved practical,

normal, increased or low, and the fluid portion relatively decreased. Oligemia, oligemia and oligohemia are synonymous, meaning "a deficiency in the amount of blood in the body," there is nothing to indicate whether the decrease is due to a relative or to an absolute diminution of fluids or of cells or both. In other words, a terminology to indicate the volume status should include information not solely of the blood mass, but also of the volume of the plasma and cells, as both may be normal or abnormal. The existent terms relative to quantity of blood are inadequate and ambiguous and were coined at a time when the volume status of the blood, plasma and cells did not enter into consideration. If one attempts to describe the volume status of the blood, plasma and cells without a concise terminology, a large number of words are necessary. For example, to describe a condition of increased volume of blood and anemia, the following definition is necessary: an increased volume of blood with a decreased ratio of the volume of cells to the volume of plasma. According to the new terminology, this would be oligocythemmic hypervolemia. As the volume of the blood, cells and plasma are shown to vary in diseased states and are probably important in the correct physiologic interpretation of basic disturbances in some instances, a concise, accurate group of terms is necessary. Therefore the proposed nomenclature is offered.

8 Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16**: 547 (Oct.) 1915.

and its inherent errors are known. The criticisms of the dye method have been summarized and discussed in a current publication. After further experimental work, and a larger clinical experience, we feel that most of the objections raised are invalid, and that the method is sufficiently accurate to determine the volume of the circulating plasma and blood in health and in disease. Sufficient work has been carried out in normal subjects to show that the volume of the blood and plasma is maintained within rather narrow limits. Variations in values are shown in many diseases, these changes correlate closely with the anticipated variations, and are of sufficient magnitude to indicate that they cannot be accounted for by defects in the method.

The method used in our determination is essentially that of Keith, Rowntree and Geraghty, except that congo red instead of vital red was used because of its availability. The optimal time for withdrawal of blood after the injection of the dye was between three and six minutes. The loss of dye from the blood within this time is negligible.

We have found no basis in fact for Lindhard's⁹ criticisms of the method. His criticisms of congo red have been carefully investigated by a series of experiments which will be discussed in detail in a subsequent publication. Suffice it to state that we were not able to substantiate his claims concerning the adsorption of the dye by the erythrocytes. Concentration from twenty to thirty times that used in the method is necessary before demonstrable amounts are taken up by the cells. His other criticism of the method relating to the variations in the concentration of the dye in the different veins and the effects of exercise on the volume of blood have been considered, and his experiments have been repeated. Our work indicates that variations in the values of the volume of blood based on determinations made simultaneously on the right and left arms do not exceed 2 per cent, a variation less than the accepted error in the method. While exercise may introduce an extraneous factor, which, like other factors, may influence the volume of the blood, it does not enter into consideration of the volume of the blood under basal or resting conditions, in which our comparative studies have been made. Because of the difference in the result of Lindhard's experiments and our own, we must conclude that differences exist in the various dye preparations on the market. We have used the American made brand of congo red purchased in the open market, and have tested it in animals for toxicity, and for abnormal absorptive properties on human blood *in vitro* before employing it in our clinical studies.

⁹ Lindhard, J. A Dye Method for Determining Blood Volume in Man, *Am J Physiol* **77** 669, 1926

Bennhold's¹⁰ observation of the rapid disappearance of congo red from the circulation in cases of pure nephrosis and amyloid disease has been confirmed by Bookman and Rosenthal¹¹ and by us. Bookman and Rosenthal noted a loss of from 47 to 55 per cent of dye in one hour. In four determinations in three cases of nephrosis, we have seen a loss of from 11 to 36 per cent in one hour, as contrasted with Bennhold's 11 to 30 per cent for normal subjects. His data do not show whether the loss is more rapid within the three to six minute interval. In four cases of nephrosis, dye appeared in the urine within ten minutes after injection, but the rate of disappearance of the dye in the serum for the three, four and six minute intervals has averaged only about 1.5 per cent greater than the normal time of disappearance (table 1).

Normal Values by the Dye Method—The normal values for the volume of blood under resting conditions have been compiled from Keith, Rowntree and Geraghty's data on eighteen subjects and from those on

TABLE 1—*Volume of Plasma in Nephrosis with Loss of Dye in the Urine Within Ten Minutes After Injection*

| Case | Two Minutes* | Three Minutes | Four Minutes | Six Minutes |
|-----------------|--------------|---------------|--------------|-------------|
| 1 | 100 | 100 | 103 | 103 |
| 2 | 100 | 97 | 100 | 100 |
| 3 | 100 | 100 | 103 | 103 |
| 4 | 100 | 100 | 100.2 | 100.2 |
| Twenty† | 100 | 100.6 | 101.5 | 101.4 |
| Normal subjects | | ±0.5 | ±0.6 | ±0.5 |

* The value for the two minute period is arbitrarily given as 100. The values for other periods represent the percentage variation from the two minute period.

† Mean values with probable error.

thirty-eight normal subjects of our own series. The ages varied from 15 to 70 years. The mean or average normal volume of blood, calculated for each kilogram of body weight, was 89.1 ± 0.6 cc or $3,383 \pm 33$ cc for each square meter of surface area. Ninety-eight per cent of our normal volume values varied between 70 and 100 cc for each kilogram. The mean volume of plasma was 50 ± 0.5 cc for each kilogram of weight or $1,973 \pm 20$ cc for each square meter. Ninety-six of the values of the volume of normal plasma varied between 40 and 60 cc. Determination of the correlation coefficients by statistical methods indicates a slightly higher relationship of the volume of blood to surface area than to the weight of the body in the group with normal weight. In

10 Bennhold, Herm. Ueber die Adsorptionsfähigkeit der Serumkolloide tubular Nierenkranken gegenüber Farbstoffen, *Ztschr f d ges exper Med* 49 71, 1926.

11 Bookman, Arthur, and Rosenthal, Julius. The Clinical Value of Intravenous Injection of Congo Red in the Diagnosis of Amyloid Disease, *Am J M Sc* 173 396, 1927.

obese subjects, the correlation coefficient of the volume of the blood to the weight of the body and the surface area is essentially the same

Data Obtained on Edema by the Dye Method—A number of workers have studied the volume of the blood and plasma in cases of edema of different types. Keith, Rowntree and Geaghty in their original report found normal values for plasma volume in cases of edema of glomerular nephritis. Bock¹² found a normal volume of plasma according to the body weight in cases of glomerular nephritis with edema. He noted the relative constancy of the volume of the plasma during different stages of edema. Brown and Roth¹³ showed that the decrease of hemoglobin and erythrocytes in chronic glomerular nephritis was due to an absolute and not to a percentage change. The volumes of blood and of plasma were similar to those observed in the usual cases of secondary anemia. Linder, Lundsgaard and Van Slyke¹⁴ found that the reduction in concentration of the plasma proteins that is observed in certain patients with nephritis is due to an actual decrease in the amount of these substances. They found normal volume of blood even in cases of extreme edema. We have¹⁵ reported observations in cases of edema of different types. We studied the volume of the blood and plasma in glomerular nephritis before and after the disappearance of the edema. Low values for the $\frac{\text{blood volume}}{\text{body weight}}$ with decreased cell to plasma volume ratios ("oligocythemic hypovolemia") were found during edema. The $\frac{\text{plasma volume}}{\text{body weight}}$ showed normal values. The changes following diuresis were inconstant and not marked. In three cases of nephrosis with edema, simple "normovolemia" or "oligocythemic hypervolemia" was present.

PRESENT STUDY

This study was based on twelve cases of acute and subacute glomerular nephritis and on nine cases of pure or mixed types of nephrosis, all showing marked grades of edema. The diagnosis of nephrosis was based on the presence of marked albuminuria, generalized edema, a decrease in the proteins in the blood and an increase in the values for lipoids and for the globulin in the serum. Hypertension, definite anemia and the usual cardiovascular changes observed in glomerular nephritis are lacking in the pure forms of nephrosis. The

12 Bock, A. V. The Constancy of the Volume of Blood Plasma, *Arch. Int. Med.* **27** 83 (Jan.) 1921.

13 Brown, G. E., and Roth, G. M. The Anemia of Chronic Nephritis, *Arch. Int. Med.* **30** 817 (Dec.) 1922.

14 Linder, G. C., Lundsgaard, C., and Van Slyke, D. D. The Concentration of the Plasma Proteins in Nephritis, *J. Exper. Med.* **39** 887, 1924.

15 Brown, G. E., and Rowntree, L. G. The Volume and Composition of the Blood and the Changes Incident to Diuresis, in Cases of Edema, *Arch. Int. Med.* **35** 129 (Jan.) 1925.

mixed forms as described by Volhard, with some features of glomerular nephritis, are the usual types observed. These usually progress and eventually may present the typical picture and termination of glomerular nephritis. Determinations of the volume of blood were made during the period of maximal edema and after diuresis. The treatment included the usual measures, a diet that contained little salt and fluid and the administration of massive doses of calcium and ammonium salts. During the last two years, we have employed injections of merbaphen (novasurol).

TABLE 2—*Volume of Blood and of Plasma in Glomerular Nephritis with Edema*

| Case | Sex | Age | Hemo- globin, Gm per 100 Cc | Per- cent- age of Cells by Hem- ato- crit | Blood | | | Plasma | | | Grade of Edema | Remarks |
|------|-----|-----|--|---|--------------------|---|---|--------------------|---|---|----------------------|--|
| | | | | | Vol- ume, Cc | Cc for Each Kg Body Weight | Cc for Each Square Meter Surface Area | Vol- ume, Cc | Cc for Each Kg of Body Weight | Cc for Each Square Meter Surface Area | | |
| 5 | M | 22 | 12.8 | 28 | 4,900 | 89 | 2,850 | 3,530 | 64 | 2,050 | 3+ | Subacute glomerular nephritis with anemia |
| 6 | M | 21 | 12.9 | 24 | 4,390 | 66 | 2,500 | 3,330 | 36 | 1,900 | 3 | Generalized edema, ascites |
| 7 | F | 17 | 13.7 | 36 | 5,210 | 80 | 2,910 | 3,330 | 51 | 1,860 | 3+ | Uremia, pulmonary edema |
| 8 | M | 15 | 10.7 | 31 | 3,620 | 70 | | 2,500 | 48 | | 4 | Ascites |
| 9 | M | 46 | 12.8 | 27 | 4,740 | 59 | 2,370 | 3,460 | 43 | 1,730 | 2+ | Progressive edema and anemia |
| 10 | F | 25 | 12.6 | 25 | 3,050 | 58 | 2,130 | 2,280 | 44 | 1,600 | 3+ | Ascites |
| 11 | F | 16 | 12.7 | 35 | 3,900 | 59 | 2,050 | 2,540 | 38 | 1,340 | 3 | Acute flare up of chronic glomerular nephritis |
| 12 | M | 20 | 14.9 | 31 | 4,540 | 75 | 2,680 | 3,130 | 52 | 1,850 | 1 | Acute nephritis, pneumonia |
| 13 | M | 17 | 6.2 | 11 | 4,050 | 71 | 2,440 | 3,600 | 63 | 2,150 | 2 | Acute nephritis mastoiditis |
| 14 | M | 20 | 17.6 | 41 | 7,010 | 93 | 4,220 | 4,140 | 55 | 2,500 | 2 | Acute nephritis, one month duration |
| 15 | M | 20 | 9.4 | 28 | 4,580 | 75 | 2,760 | 3,300 | 54 | 1,930 | 2 | Some elements of nephrosis |
| 16 | F | 26 | 9.7 | 33 | 4,835 | 105 | | 3,240 | 70 | | 3 | Subacute nephritis |

Mean Values: blood volume = 74.5 ± 3 cc for each Kg of body weight or $2,719.5 \pm 123$ cc for each square meter, plasma volume = 51.9 ± 2 cc for each Kg of body weight or $1,899.5 \pm 63$ cc for each square meter, hemoglobin = 12.12 ± 5.1 Gm percentage, percentage of cells by the hematocrit = 29.5 ± 1 .

with or without the administration of calcium and ammonium salts in cases in which there has not been retention of nitrogen. Paracentesis was performed in several cases.

The volume of the blood was calculated on the basis of the body weight of the edema-free period, designated as the corrected body weight. The volume on the basis of surface area is also given. The surface area was calculated according to the DuBois standards and for the corrected body weight. The data on the volume in eighteen cases of secondary anemia and ten cases of pernicious anemia were used as a contrast group.

Glomerular Nephritis with Edema—The mean volume of blood (table 2) with its probable error for the group was 74.5 ± 3 cc for each kilogram of corrected body weight, that is, 15 cc for each kilogram less than normal, or $2,719.5 \pm 123$ cc for each square meter. The range was

from 58 to 93 cc for each kilogram or from 2,050 to 4,220 cc for each square meter. The mean volume of plasma was practically normal, 51.9 ± 2 cc for each kilogram or $1,899.5 \pm 63$ cc for each square meter. The range was from 36 to 64 cc. The mean percentage of cells as shown

TABLE 3—*The Volume of Blood and Plasma in the Edema, Edema-Free and Recovery Periods in Subacute Glomerular Nephritis*

| Case | Date | Hemo- globin, Gm per 100 Cc | Per- cent- age of Cells by Hem- ato- crit | Vol- ume, Cc | Blood, Cc for Each Kg of Body Weight* | | Vol- ume, Cc | Plasma, Cc for Each Kg of Body Weight | | Body Weight, Kg | Remarks |
|------|----------|--|---|--------------------|--|----------------|--------------------|--|----------------|-----------------------|--|
| | | | | | Uncor- rected | Cor- rected | | Uncor- rected | Cor- rected | | |
| 5 | 12/ 3/25 | 12.8 | 28 | 4,900 | 54 | 73 | 3,530 | 39 | 53 | 90 | Edema graded 3 |
| | 12/22/25 | 12.8 | 30 | 4,150 | 52 | 62 | 2,910 | 38 | 43 | 80 | Edema graded 2 |
| | 1/25/26 | 14.3 | 30 | 4,320 | 72 | 64 | 3,020 | 50 | 45 | 60 | Edema free |
| | 11/24/26 | 13.8 | 35 | 5,720 | 86 | 86 | 3,710 | 56 | 56 | 67 | Patient fairly well 11 months later |
| 6 | 8/ 7/23 | 12.4 | 24 | 4,390 | 48 | 68 | 3,300 | 36 | 51 | 90 | Edema graded 3 |
| | 9/11/23 | 12.9 | 29 | 4,100 | 62 | 62 | 2,930 | 45 | 45 | 64 | Edema |
| 10 | 11/15/22 | 12.6 | 25 | 3,050 | 50 | 61 | 2,280 | 37 | 46 | 61 | Edema graded 3, anemia, ascites |
| | 1/ 5/23 | 8.0 | 19 | 3,200 | 66 | 64 | 2,590 | 54 | 52 | 50 | Edema free |
| | 9/ 6/23 | 17.0 | 37 | 4,620 | 89 | 89 | 2,910 | 55 | 53 | 52 | Apparently recovered |
| 13 | 6/ 2/23 | 6.2 | 11 | 1,050 | 62 | 72 | 3,600 | 55 | 64 | 65 | Acute nephritis, edema 3 |
| | 7/ 3/23 | 8.1 | 20 | 3,300 | 60 | 60 | 2,640 | 47 | 47 | 56 | Edema graded 1 |
| 14 | 2/20/23 | 17.6 | 41 | 7,010 | 84 | 91 | 4,140 | 49 | 55 | 83 | Acute nephritis, edema 3 |
| | 3/ 1/23 | 17.3 | 42 | 6,900 | 97 | 90 | 4,000 | 56 | 54 | 71 | Edema free |
| | 5/16/23 | 17.0 | 40 | 6,860 | 92 | 90 | 4,120 | 55 | 55 | 75 | Edema free |
| | 12/12/23 | 18.5 | 45 | 7,190 | 95 | 95 | 3,950 | 52 | 52 | 75 | Good recovery, no edema |
| 16 | 4/ 6/27 | 9.7 | 33 | 4,835 | 78 | 105 | 3,240 | 52 | 70 | 62 | Edema graded 3 |
| | 5/ 3/27 | 11.0 | 20 | 4,250 | | 91 | 3,390 | | 73 | 46 | Weight loss, both fluid and body protein |

* Body weight in the postedema period = corrected body weight, body weight in the edema period = uncorrected body weight

TABLE 4—*Summary of Changes in the Volume of the Blood and of Plasma Occurring During Diuresis in Glomerular Nephritis*

| Case | Weight Loss, Kg | Percentage Change of Cells by Hematocrit | Blood Volume | | Plasma Volume | | Duration of Time for Diuresis, Days |
|------|-----------------------|---|-----------------|-----------------|-----------------|-----------------|--|
| | | | Increase, Cc | Decrease, Cc | Increase, Cc | Decrease, Cc | |
| 5 | 30 | +2 | | 580 | | 500 | 63 |
| 6 | 27 | +5 | | 290 | | 370 | 34 |
| 7 | 2.5 | -9 | | 910 | | 170 | 14 |
| 9 | 8.5 | -13 | | 2,090 | | 830 | 83 |
| 10 | 14 | -6 | 150 | | 310 | | 50 |
| 13 | 9 | +9 | | 750 | | 960 | 31 |
| 14 | 10 | | | 100 | | 150 | 11 |
| 16 | 16 | -13 | | 585 | 155 | | 27 |

by the hematocrit was 29.5 ± 1 (the normal value is 42 per cent) and the hemoglobin in grams per hundred cubic centimeters of blood was 12.1 ± 5.1 as contrasted with the normal value, 15.6 per cent¹⁶. The mean values in this study corroborate our original claim that "oligocythemmic hypovolemia" characterizes glomerular nephritis.

Changes During Diuresis in Chronic Glomerular Nephritis—The variations in the volume of the blood and plasma during diuresis are shown in table 3. A summary of the changes occurring in eight cases with two or more determinations of volume during the period of treatment are shown in table 4. There is a fairly constant directional change in the volume of blood during the period of diuresis, as seven of the eight cases showed a decrease in the volume of blood. In case 5 there was a loss of 500 cc in the volume of the blood, which was entirely due to a loss in plasma, in case 6 there was a decrease of 370 cc of plasma, in case 7, there was a large loss in the volume of blood, which was

TABLE 5—*The Volume of the Blood and of Plasma in Nephrosis, Edema Stage*

| Case | Sex | Age | Hemo- globin, Gm per 100 Cc | Per cent age of Cells by Hema- to- crit | Blood | | | Plasma | | | Edema, Grade 1-4 | Remarks |
|------|-----|-----|--|---|--------------------|---|---|--------------------|---|---|------------------------|--|
| | | | | | Vol- ume, Cc | Cc for Each Kg Body Weight | Cc for Each Square Meter Surface Area | Vol- ume, Cc | Cc for Each Kg Body Weight | Cc for Each Square Meter Surface Area | | |
| 1 | M | 23 | 15.9 | 50 | 5,750 | 84 | | 2,875 | 42 | | 3+ | Probably a case of pure nephrosis |
| 4 | F | 25 | 11.6 | 39 | 4,665 | 103 | | 2,845 | 64 | | 3+ | Nephrosis with some features of glomerular involvement |
| 9 | M | 46 | 18.6 | 38 | 6,830 | 81 | 3,500 | 4,240 | 50 | 2,170 | 1 | Nephrosis picture, at this stage |
| 17 | M | 37 | 19.6 | 45 | 6,680 | 89 | 3,630 | 3,670 | 49 | 2,000 | 2 | ascites 2, mixed nephrosis |
| 18 | M | 33 | 19.8 | 44 | 7,100 | 102 | | 2,860 | 57 | | 2 | Emaciated |
| 19 | M | 25 | 17.0 | 39 | 5,370 | 93 | 3,210 | 3,270 | 56 | 1,950 | 2 | Generalized edema |
| 20 | M | 32 | 12.3 | 30 | 5,780 | 101 | 3,450 | 4,050 | 71 | 2,420 | 2 3 | Mixed lesions, glomerular nephritis |
| 21 | M | 31 | 12.5 | 35 | 4,850 | 99 | 3,070 | 3,240 | 66 | 2,050 | 1+ | Mild nephrosis |
| 22 | M | 19 | 14.2 | 24 | 6,010 | 105 | 3,800 | 4,570 | 80 | 2,710 | 2+ | Nephrosis and Pott's disease |

Mean Values blood volume = 94.8 ± 2 cc for each Kg or $3,449.5 \pm 60$ cc for each square meter, plasma volume = 60.0 ± 3 cc for each Kg or $2,123.5 \pm 81$ cc for each square meter, hemoglobin = 15.7 ± 7.2 Gm percentage, percentage of cells by the hematocrit = 37.5 ± 2

almost entirely due to cells, in case 9, there was a huge decrease in the blood mass, two thirds of which was cells, in case 10, there were not any significant changes, in case thirteen, there was a loss of 960 cc of plasma. The changes were not significant in case 14. In case 16, the volume of blood decreased 580 cc, which was largely a decrease in cells. The loss in weight due to diuresis varied in these subjects from 2.5 to 30 Kg. The duration of treatment varied from six to ninety days.

Nephrosis—On the basis of the corrected body weight, the mean volume of blood during the stage of edema in nine cases of nephrosis was 94.8 ± 2 cc for each kilogram or 5 cc more than the normal mean, or $3,449 \pm 60$ cc for each square meter of surface area. These figures for the mean value are still within the normal upper range. The variation in the group was from 81 to 105 cc for each kilogram or 3,070 to

3,800 cc according to area. The mean volume of plasma was 60 ± 3 cc or 10 cc (20 per cent) more than the normal, and $2,123.5 \pm 81$ cc according to weight and surface area, respectively, or 150 cc more than normal. The variations were from 49 to 80 cc for weight and 1,950 to 2,710 cc for surface area. The mean hemoglobin content in grams per hundred cubic centimeters of blood was 15.7 ± 7.2 and the mean percentage of cells as shown by the hematocrit was 37.5 ± 2 . A mild grade of anemia was present in four cases.

A study of these mean values indicates that there is a moderate increase in the mean total volume of blood and a definite increase in the mean volume of plasma as compared to the normal. This would be interpreted as "oligocythemmic hypervolemia." Although the mean values are high, five of the nine cases showed values that were strictly normal, "normovolemia simplex." It would appear that in cases of nephrosis with edema, the volume of blood and of plasma tends to become

TABLE 6—*Changes in the Volume of Blood and of Plasma with Diuresis in Cases of Nephrosis*

| Case | Weight Loss, Kg | Percentage of Cells by the Hematocrit Changes | Blood Decrease, Cc | Plasma | | Duration of Dehydration Period, Days |
|------|-----------------|---|--------------------|--------------|--------------|--------------------------------------|
| | | | | Increase, Cc | Decrease, Cc | |
| 1 | 8 | -7 | | 305 | | 11 |
| 4 | 15 | -7 | 105 | 255 | | 16 |
| 9 | 4 | -3 | 300 | | | 30 |
| 17 | 10 | -1 | | | | 22 |
| 19 | 15 | -2 | | | | 24 |
| 22 | 9 | +1 | 600 | | 400 | 13 |

increased. It is also interesting that in the four cases with the largest volume of plasma some evidence of anemia was shown by the decreased values for hemoglobin, and percentage of cells by the hematocrit. It is evident, therefore, that nephrosis with edema may be associated with normal or increased volume of blood and of plasma, "simple normovolemia" or "oligocythemmic hypervolemia."

Table 6 gives the summarized data of the changes that occur in blood and plasma with diuresis in nephrosis. In only one case, case 22, were significant changes observed. A loss of 600 cc of blood occurred, 400 cc of which was due to a decrease in the plasma. In case 1, there was a slight loss in plasma. Control of the edema, therefore, does not appear to influence the volume of blood to any appreciable degree.

Changes Observed in Nephrosis When the Signs and Symptoms of Glomerular Nephritis Subsequently Develop—Data concerning the volume of blood in case 9, which when first observed presented a classic example of nephrosis, are given in table 7. The blood pressure was normal and the blood cholesterol high, while the protein in the serum was reduced. The volume of the blood was 81 cc for each kilogram of

normal weight,¹⁷ the volume of plasma was 53 cc. This was during the period of maximal general anasarca and ascites. The hemoglobin in grams per hundred cubic centimeters was 18.6, and there was 38 per cent of cells, as ascertained by the hematocrit. During a period of two months, the edema fluctuated, various forms of treatment were used: desiccated thyroid, massive doses of calcium and later abdominal paracentesis. The hemoglobin showed a gradual reduction comparable to the reduction in the volume of cells. The total volume of blood decreased to 59 cc for each kilogram, and the volume of plasma decreased to 42 cc for each kilogram. At the final examination, retention of urea had developed, the blood pressure had increased, and glomerular nephritis was evident. The

TABLE 7—*Nephrosis Subsequent Development of Subacute Glomerular Nephritis with Anemia*

| Case | Date | Hemo- globin, Gm per 100 Cc | Per- centage Hemo- globin, by Hema- tocrit | Blood | | Plasma | | | Comment |
|------|----------|--------------------------------------|---|---|-----------------|---|-----------------|-----------------------|------------------------|
| | | | | Cc for Each Kg Body Weight, Volume, Cc | Cor- rected* | Cc for Each Kg Body Weight, Volume, Cc | Cor- rected* | Body Weight, Kg | |
| 9 | 10/ 7/22 | 18.6 | 38 | 6,830 | 81 | 4,240 | 53 | 94 | Marked edema, ascites |
| | 10/17/22 | 17.0 | 43 | 7,340 | 91 | 4,190 | 52 | 90 | Some dye in urine |
| | 10/21/22 | 17.0 | 35 | 6,220 | 78 | 4,040 | 51 | 90 | |
| | 11/ 7/22 | 16.8 | 40 | 5,710 | 71 | 3,460 | 43 | 90 | |
| | 11/17/22 | 13.3 | 35 | 6,510 | 81 | 4,240 | 53 | 87 | Paracentesis abdominis |
| | 11/29/22 | 13.1 | 37 | 6,720 | 84 | 4,240 | 53 | 86 | |
| | 12/ 7/22 | 13.8 | 28 | 4,910 | 63 | 3,830 | 48 | 90 | |
| | 12/13/22 | 12.8 | 27 | 4,740 | 50 | 3,460 | 43 | 89 | |
| | 12/23/22 | 10.9 | 28 | 5,210 | 65 | 3,750 | 47 | 90 | |
| | 12/30/22 | 9.6 | 29 | 4,740 | 59 | 3,360 | 42 | 86 | Edema 2, ascites 1 |

* Weight corrected on the basis of his normal weight, 80 Kg

volume of blood and of plasma had decreased materially, but it did not show any fluctuations that were related to the fluctuation in the degree of edema, but preceded paripassu with the progressing anemia.

Data on Volume of Blood in Glomerular Nephritis—There is no evidence that dilution of the blood occurs in subjects with the edema that accompanies glomerular nephritis. When calculated on the basis of the corrected body weight, a normal or a decreased volume ("normovolemia or hypovolemia") is the rule. On the basis of the changes in the blood, cases of glomerular nephritis can be divided into two groups: those in which there is anemia and those in which anemia does not occur. The latter group consists largely of cases of the mild and of the more acute forms of the disease. In the subacute or chronic stages anemia is almost uniformly present in some degree. The pallor of these subjects, the decreased specific gravity of the blood and the decrease in erythrocytes,

17 This patient never became free from edema, and his usual normal weight was used as the corrected body weight.

in the presence of edema, seem at first sight evidence of blood dilution. These changes, however, are similar to those found in simple chronic anemia without edema. The anemia in nephritis is due to an absolute decrease in erythrocytes, since the volume of plasma is not increased to produce dilution or an apparent anemia. The lowered specific gravity of the plasma and decreased percentage of protein have been shown to

TABLE 8—*Mean Values with Probable Error*

| Group | Case | Hemo- globin, Gm per 100 Cc | Per- centage of Cells by Hema- toerit | Volume of Blood | | Range | Cc for Each Kg of Weight | Cc for Each Square Meter of Area | Range |
|---------------------------------|------|--------------------------------------|---|---|---|--------|---|---|-------|
| | | | | Cc for Each Kg of Weight | Cc for Each Square Meter of Area | | | | |
| Glomerular nephritis with edema | 12 | 12.1 ± 5.1 | 29.5 ± 1 | 74.5 ± 3 | 2719.5 ± 123 | 58-93 | 51.9 ± 2 | 1889.5 ± 63 | 36-64 |
| Nephrosis with edema | 9 | 15.7 ± 7.2 | 37.5 ± 2 | 94.8 ± 2 | 3449.5 ± 60 | 81-105 | 60.0 ± 3 | 2123.5 ± 51 | 49-80 |
| Chronic secondary anemia | 18 | 11.45 ± 4.3 | 30.5 ± 9.6 | 82.8 ± 2.9 | 2705.5 ± 94.2 | 50-110 | 56.7 ± 1.9 | 1997.5 ± 95.3 | 34-76 |
| Permeious anemia | 10 | 11.0 ± 5.2 | 22.6 ± 14.4 | 77.0 ± 1.7 | 2771.7 ± 42 | 65-90 | 60.2 ± 1.1 | 2194 ± 47.5 | 50-68 |
| Normal* | 56 | 17.8 ± 0.2 | 42.1 ± 2 | 89.1 ± 0.6 | 3383 ± 33 | 70-100 | 50 ± 0.5 | 1973 ± 20 | 40-60 |

* This group is not a representative normal group but is composed of a selected group of normal adults, most of whom were males.

TABLE 9—*Blood and Plasma Volume in Polycythemia Vera Under Treatment with Phenylhydrazine Hydrochloride*

| Case | Date | Hemo- globin, Gm per 100 Cc | Hema- toerit, Cells, per Cent | Volume of Blood | | Volume of Plasma | |
|------|----------|--------------------------------------|--|-----------------|-------------------|------------------|-------------------|
| | | | | Total, Cc. | Cc for Each Kg | Total, Cc | Cc for Each kg |
| 23 | 12/15/24 | 22.5 | 67 | 11,000 | 183 | 3,636 | 60 |
| | 12/28/24 | 21.4 | 63 | 7,973 | 142 | 2,950 | 52 |
| | 1/7/25 | 18.1 | 63 | 10,800 | 189 | 4,000 | 70 |
| | 1/14/25 | 19.9 | 65 | 9,900 | 173 | 3,460 | 60 |
| | 2/4/25 | 16 | 56 | 8,520 | 157 | 3,750 | 69 |
| | 2/11/25 | 12.4 | 40 | 6,510 | 116 | 3,910 | 70 |
| | 2/16/25 | 11.5 | 39 | 5,800 | 103 | 3,580 | 63 |
| 24 | | 26 | 75 | 14,700 | 180 | 3,675 | 46 |
| | 12/23/25 | | 43 | 6,940 | 90 | 3,955 | 52 |
| | 1/4/26 | | 24 | 5,650 | 75 | 4,290 | 57 |
| 25 | 11/14/25 | 4.5 | 60 | 8,580 | 136 | 3,430 | 54 |
| | 12/7/25 | 12.8 | 32 | 4,514 | 71 | 3,076 | 48 |
| 26 | 8/10/25 | 24 | 59 | 8,607 | 136 | 3,529 | 55 |
| | 8/17/25 | | 37 | 5,952 | 93 | 5,750 | 58 |
| | 8/28/25 | 5.7 | | 5,500 | 87 | 4,675 | 72 |

be due to an absolute loss of albumin in the blood. Our data show that the mean volume of blood in glomerular nephritis, when corrected for the edema-free body weight, is less than normal, while the mean volume of plasma is quite normal ("oligocythemic hypovolemia"). The decrease in the total volume depends on the decreased volume of cells and indicates true anemia.

Plasma Cell Relationships in Anemia—As is known, in certain forms of anemia a replacement compensatory or restoration process occurs to maintain an adequate volume of blood. Plasma enters the blood quickly following bleeding, while replacement of cells occurs more slowly. In the chronic types of anemia, in which cells are reduced without loss of plasma, the mechanism is variable. Studies of the volumes of blood and of plasma in the simple and primary types of anemia show definite differences in these two forms (table 8). It will be observed from the data that the mean volume of plasma in eighteen cases of chronic secondary anemia is 56.7 ± 1.9 cc for each kilogram of body weight. This is above the normal value, while the relative absolute volume of blood is moderately reduced, 82.8 ± 2.9 , owing to the diminished volume of cells. It is apparent that replacement of cells by plasma is moderate. It was found that in ten subjects with pernicious anemia, the mean volume of plasma was 60 cc for each kilogram of body weight. The total volume of blood and of cells was lower than in secondary anemia, since the degree of anemia was more marked. The higher values for the volume of plasma would indicate that in pernicious anemia there was a partial replacement of cells by plasma. Similar high volumes of plasma were found by Keith¹⁸ in twelve cases of pernicious anemia. In one of the cases with a decrease in the hemoglobin of 20 per cent and in the percentage of cells of 40 per cent as determined by the hematocrit, the volume of plasma increased 9 cc for each kilogram of body weight, or approximately 15 per cent over the former volume of plasma. In one case in which the hemoglobin and erythrocytes were increasing, there was a reduction in the relative plasma to offset the increased volume of cells. This difference of response of the replacement mechanism in different forms of anemia is of interest and requires further investigation. We have obtained further information concerning the response of the plasma to loss of cells in cases of polycythemia vera in which the patient is treated with phenylhydrazine. With this form of treatment there is rapid destruction of erythrocytes within a few days. The volumes of the blood and of the plasma during the period of destruction of the blood are shown in table 9. Within fifty days, there was a decrease of 6.5 Gm of hemoglobin for each 100 cc of blood in case 23 and a decrease of 11 in the percentage of cells as shown by the hematocrit with an increase of 9 cc of plasma for each kilogram of body weight, or approximately 15 per cent. With further reduction in the volume of cells and of hemoglobin, there was no further increase in the volume of the plasma. Similar increases in the volume of the plasma were observed in cases 24 and 26.

18 Keith, N. M. Total Circulating Volume of Blood and Plasma in Chronic Anemia and Leukemia, *Am J M Sc* **165** 174, 1923

Comparing the data concerning the volume of blood in the cases of glomerular nephritis accompanied by edema and anemia with these in cases of secondary anemia, a definite dissimilarity is apparent (chart 2). The mean volume of plasma in the cases of glomerular nephritis is lower than in secondary anemia, and the grade of anemia is comparable for both groups. The replacement of cells by plasma does not occur or at least is not maintained and diuresis per se produces no significant variations in the volume of blood and plasma in cases of glomerular nephritis.

The changes occurring in the volume of blood during diuresis in glomerular nephritis are largely those due to further decrease in the

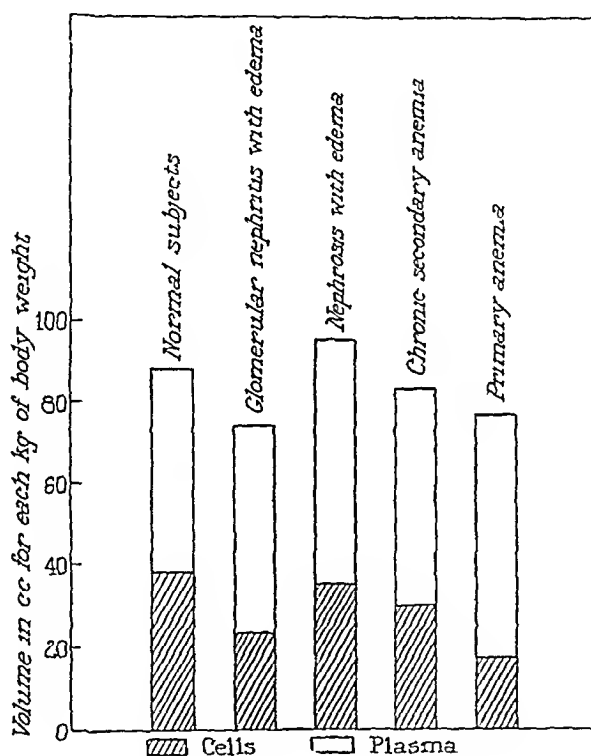


Chart 2—Mean volumes of the blood, according to body weight, in glomerular nephritis, nephrosis and chronic anemia. The diagonal lines indicate the blood cells and the blank spaces the blood plasma.

volume of cells, indicating that progressive anemia is developing during the period of diuresis. This is not due to dilution, since the volume of plasma maintains a fairly constant level while the volume of cells is progressively diminishing. Restoration of the volume of blood by plasma does not occur. The proof of this is given in case 9 in which the studies of volume were carried out during the period of the development of the anemia or during the transition stage from what was apparently a case of nephrosis to true glomerular nephritis. The constancy of the relation of the volume of plasma to body weight during the period of developing anemia and fluctuating edema is quite evident. The relative volume of

plasma remained fairly constant until the anemia was definitely present or until the hemoglobin had become reduced to 12.8 Gm per hundred cubic centimeters. With further reduction of the hemoglobin to 9.6 Gm per 100 cubic centimeters, there was a decrease in the volume of the plasma of 6 cc for each kilogram of body weight. This variation in the volume of plasma could not be correlated to fluctuations in the amount of edema.

Data on the Volume of the Blood in Nephrosis—Anemia is not marked or constant in nephrosis. Elwyn stated that "moderate anemia is present averaging 4,000,000 erythrocytes for each centimeter and that with the disappearance of edema temporary blood dilution with an increased anemia occurs." Our data show that in five of the nine cases the hemoglobin values and those obtained by the hematocrit were normal, in the remaining four cases, there was a mild degree of anemia. The mean hemoglobin in grams per hundred cubic centimeters was 15.7 ± 7.2 , and the mean percentage of cells as ascertained by the hematocrit was 37.5 ± 2 . In the cases without anemia the average volume of blood was 88 cc for each kilogram, and the average volume of plasma was 51 cc for each kilogram. These volumes are quite normal. In the four cases of mild anemia, the average volume of blood was 102 cc for each kilogram of body weight, and the amount of plasma was 70 cc for each kilogram. Taking the group as a whole, the mean volume of blood in cases of nephrosis is about 5 cc higher than the normal mean and 20 cc higher than the mean in glomerular nephritis (table 8, chart 2). When the mean values of the entire group are compared with those in non-nephritic chronic secondary anemia, the mean volume of blood and plasma is 12 cc and 3.3 cc, respectively, greater in the cases of nephrosis, as compared to primary or pernicious anemia, the mean volume of blood is 17 cc higher in the group of cases of nephrosis, while the volume of plasma is identical in the two groups.

If the cases of nephrosis with anemia are compared with those of chronic secondary anemia and pernicious anemia, it is apparent that both the volume of blood and the volume of plasma are definitely greater, while the degree of anemia is less in the cases of nephrosis.

These data are quite different from those in glomerular nephritis, the volume of cells is only slightly decreased in the cases of nephrosis, while in glomerular nephritis it is markedly lowered, and the mean volume of plasma is about 10 cc higher in nephrosis than in glomerular nephritis. The explanation for this dissimilarity is not entirely clear. One would be tempted to assume that the relatively high volume of plasma in nephrosis represents an example of blood dilution, and that the increased volume of plasma, which is about 20 per cent, would be sufficient to produce apparent or dilution anemia. An argument against this is the slight or negligible changes occurring in the volume of blood and of plasma with diuresis. In only one case was definite variation

observed, a decrease of 600 cc of whole blood, of which two-thirds was due to decrease in the plasma. In the other cases, the changes were slight and did not show a constant directional tendency.

It could also be assumed that when true mild anemia is present in some cases of nephrosis that the replacement of cells by plasma is more than adequate. The objection to this hypothesis rests on the fact that our data show the mean volume of blood and of plasma in cases of nephrosis with anemia to be 13 cc and 20 cc higher, respectively, than the normal mean. Restoration of blood mass by plasma in response to loss of cells would then be excessive, a conception that is difficult to explain. The loss of dye in the urine in cases of nephrosis, if sufficient to produce an abnormal or too rapid disappearance of the dye in the blood serum, would give an abnormally high or false volume of plasma. We studied the rates of disappearance of the dye in the blood serum in four cases of nephrosis in which dye was present in the urine within ten minutes after its injection. Table 1 shows that, as compared with the normal, there was a greater decrease in the percentage of concentration of the dye in the two to six minute interval as shown by the volume of plasma. This difference, 1.5 per cent, appears to us too small to explain fully the relatively high values of the volume of plasma in the cases of nephrosis. In order to settle the question definitely, it would be necessary to study the volumes before and during the development of the disease.

These studies on the volumes of the blood and plasma in cases of glomerular nephritis and nephrosis and primary and secondary anemia suggest the following hypothesis. The changes occurring in the plasma volume are in large part related to loss of cells. The decrease in cell volume is replaced by plasma. This replacement is usually not complete and varies in different forms of anemia. In chronic secondary anemia replacement is partially complete, but not as marked as in the primary forms and in anemia associated with splenomegaly. In glomerular nephritis with edema and a secondary type of anemia, replacement by plasma occurs to a slight extent or not at all. Edema may be an essential factor in withholding plasma from the blood. In nephrosis without anemia these factors apparently do not obtain, and the blood and plasma volumes are normal. When anemia occurs, there is an increase of plasma. As edema is common to both groups, the anemia appears to be a more critical factor than edema in determining the status of the plasma volumes.

SUMMARY

A low or low normal volume of blood is found in cases of glomerular nephritis with edema. The reduction in the volume of blood is due to a diminished volume of cells. The mean volume of plasma is normal; this indicates actual anemia. According to the new terminology, the volume

state is "oligocythemmic normovolemia" or "oligocythemmic hypovolemia". During diuresis, the significant changes in the blood volume and of plasma are those related to further reduction in the volume of cells, that is, to the progression of the anemia. In chronic nephritis with edema a form of the chronic secondary anemia due to deficient erythropoiesis is present and replacement of cells by plasma does not occur, or, at least, is not adequately maintained.

In cases of nephrosis with edema, approximately 50 per cent do not show anemia, the remainder show mild grades of anemia. In the non-anemic group, strictly normal values for the volume of blood and of plasma are obtained ("simple normovolemia"), in cases with diminished hemoglobin and cell values, the volume of blood and plasma are definitely increased, "oligocythemmic hypervolemia". The increase in the blood volume and of plasma is excessive. An explanation of this increase of blood volume and plasma by restoration of plasma is not at hand, there is no good evidence to indicate that in these cases a dilution phenomenon occurs, and diuresis does not produce any changes in the volume of blood and of plasma, which admittedly is evidence against the dilution theory. Abnormal loss of dye in the urine may account in part, but not wholly, for the increase in the volume of plasma.

These values for the volume of blood and of plasma in cases of glomerular nephritis and nephrosis accompanied by edema are comparable to those reported in our previous study of a smaller group of cases

MUMPS POLYNEURITIS

QUADRIPLÉGIA WITH BILATERAL FACIAL PARALYSIS⁺

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The neurologic complications occurring in mumps have frequently been observed and recorded. They may be classified into the following types: (1) meningitis,¹ (2) encephalitis,² and (3) neuritis: (a) second, sixth, seventh, eighth, eleventh and twelfth cranial nerves,³ (b) diffuse polyneuritis and (c) localized neuritis. An excellent review of the literature up to 1898 was made by Gallavardin,⁴ and another review to 1915 was made by Feiling.⁵

We record a unique case of polyneuritis in which all extremities of the patient were affected with bilateral facial involvement complicating epidemic parotitis. We have been able to find only four cases of diffuse polyneuritis in the literature—all were described by the French.

REVIEW OF THE LITERATURE

Joffroy⁶ was the first to call attention to this syndrome. He reported the case of a child, aged 4½ years, who, during convalescence, developed a quadriplegia three weeks after the onset of epidemic parotitis. Neurologic examination revealed a loss of all the deep and superficial reflexes, generalized superficial hypesthesia and an abolition of faradic contractility. The cranial nerves were not involved. The child began to improve about the third month, and by the fourth month almost all motor power had returned. Eleven months later, the child was found to have made a complete recovery.

Revilliod⁷ recorded the second case which was that of a child, aged 7 years, who contracted epidemic parotitis. One week after the onset of

⁺ From the Department of Medicine and the Harry Caplin Research Laboratory, Jewish Hospital.

1 Acker, G. N. Parotitis Complicated with Meningitis, *Am J Dis Child* **6** 399 (Dec) 1913.

2 Haden, R. L. The Cerebral Complications of Mumps, *Arch Int Med* **23**:737 (June) 1919.

3 Lannois. *Lyon méd* **93** 469, 1900. Roger and Magarot. *Rev méd* 1909, p 826.

4 Gallavardin, M. L. *Gaz d hôp* **71** 1329, 1898.

5 Feiling, A. *Quart J Med* **8** 257, 1915.

6 Joffroy, A. *Progrès méd*, 1886, p 1009.

7 Revilliod, L. *Rev med de la Suisse romande* **16** 752, 1896.

the mumps, the child developed a marked weakness in the legs and disturbance in deglutition. Examination revealed a quadriplegia with a loss in the superficial and deep reflexes, bilateral sixth nerve paralysis and left facial and right hypoglossal weakness. There were no sensory or trophic disorders, and the special senses were intact. One week later, the child was able to stand and by the end of two months, he had made a complete recovery.

The third case was reported by Gallavardin,⁴ that of a woman, aged 31, who developed a flaccid paralysis of all the limbs two weeks after the onset of the mumps. There was a loss of all the reflexes and deep muscle sense and a diminution in response to faradic stimulation. She made slow progressive improvement.

Pitres and Marchand⁸ record a case of quadriplegic polyneuritic paralysis occurring in a young soldier during convalescence from mumps. The paralysis appeared two weeks after the onset of mumps. There was a loss of all the reflexes and an abolition of deep muscle and stereognostic sense, the cranial nerves were not involved. The patient was still slightly incapacitated at the end of a year.

Other cases of hemiplegia and diplegia of either the upper or lower extremities of peripheral origin have also been reported.⁹

REPORT OF CASE

History—A young man, aged 29, contracted a mild attack of epidemic parotitis which subsided in five days. One week after the onset, he developed a left orchitis accompanied by chills and a temperature of 104 F. The orchitis subsided in one week, with resulting atrophy of the testicle. On May 28th, three weeks after the onset of his present illness, he complained of weakness in the lower extremities, and found that he was unable to stand. He became progressively worse, and within forty-eight hours was unable to sit or roll over in bed. He also complained of some disturbance in swallowing food.

Examination—Physical examination revealed a well developed and well nourished young man who did not appear acutely ill. He lay flat on his back, unable to move his head or his extremities. His neck was rigid, his head in slight opisthotonus. He showed a complete bilateral upper and lower facial paralysis. Difficulty in swallowing was really difficulty in ingesting food owing to his facial paralysis. All the other cranial nerves were uninvolved. There was a complete parietic quadriplegia, with greater involvement of the extensor than the flexor group of muscles, and a marked bilateral Kernig sign. He showed a loss of all the deep reflexes, nor could any superficial reflexes be elicited. All plantar reflex phenomena were absent. The sensory changes occurred twenty-four hours later, and consisted of paresthesia of the feet, such as tingling and burning sensations, hypesthesia of the arms and legs, hyperesthesia of the hands and feet and loss of joint and vibratory sense in all extremities.

8 Pitres, A and Marchand, L. *Progres med* 50 397, 1922

9 Santon and Huriez. *Bull et mem Soc med d hôp de Paris* 39 809, 1915, *Loire méd*, 1891

A lumbar puncture done on the fourth day of his neurologic complication showed clear spinal fluid under pressure, containing 18 lymphocytes per cubic millimeter. The fluid on analysis showed a 2 mm albumin ring, globulin four plus, 44 mg of sugar per hundred cubic centimeters. The Wassermann reaction was negative, the smear was negative for *Bacillus tuberculosis* or other organisms, the culture was sterile, and the colloidal gold curve was 00000000. A lumbar puncture the following day showed clear fluid under normal pressure, containing only 3 lymphocytes per cubic millimeter. The patient's urine was normal except for a faint trace of albumin.

The blood count showed hemoglobin, 85 per cent, red blood cells, 5,300,000, white blood cells, 13,000, polymorphonuclear leukocytes 56 per cent, lymphocytes 40 per cent. The blood pressure was 142 systolic and 74 diastolic.

Diagnosis—In view of the fact that there was a specific etiologic factor present to account for this symptom complex, a provisional diagnosis was made of diffuse quadriplegic polyneuritis with a bilateral peripheral facial paralysis and meningitis, arising from an epidemic parotitis.

Course of Illness—June 6, 1927 (one week later) —The patient began to show evidence of a regression of his lesion, some muscular power was returning in all extremities, and the plantar flexion phenomenon of the right foot was present.

June 10 Voluntary movement of right facial group muscles was returning. Hypesthesia of the legs was clearing up.

June 13 The patient started to receive strychnine sulphate $\frac{1}{100}$ grain (0.002 Gm) three times a day.

June 14 It was noted that the patient had made rapid improvement during the preceding twenty-four hours; the motor signs improved faster than the sensory; the abdominal reflexes were present but exhaustible.

June 18. The patient was able to raise the arms above the head. The thighs and legs could be well flexed.

June 20 The patient was discharged from the hospital in the following condition: no rigidity of the neck; slight bilateral Kernig sign present; condition of cranial nerves: could wrinkle forehead, closed eyelids poorly, smiled slightly, barely able to show his teeth; fundi normal, hearing normal, taste and smell normal, hypesthesia of anterior portion of tongue gone, movements of tongue normal, eleventh nerve normal, pharyngeal reflex present, spinal motor reactions: had good grip, flexors of arm good, right better than left, muscles of legs markedly improved, quadriceps contraction good, able to sit up with slight support but required assistance to sitting position, no drop foot, sensory reactions: superficial sense normal, slight astereognosis and ataxia of upper extremities, deep joint sense in hands and feet absent, deep muscle and pain sense present, reflexes: abdominal present, right cremasteric present, left not elicited, plantar flexion phenomenon of foot elicited on both sides, deep reflexes absent, visceral phenomena normal.

The patient had an atrophy of the left testicle. He was afebrile during the entire course of his neurologic disorder.

The patient was again seen on June 24, 1927 (four weeks after the onset of the paralysis). He was then able to stand with some assistance. Quadriceps extension could be maintained for thirty seconds. Right facial power was rapidly returning to normal. Deep reflexes and deep joint sense were still absent.

June 29th The patient was able to sit up voluntarily without support. The upper extremities possessed practically normal power. The patient was able to get out of bed and stood and took a few steps with some assistance. The quadriceps extension could be maintained for one and one-half minutes. The

left joint sense in the foot had returned although the right was still absent. The joint sense in the hands was normal. All deep reflexes were absent, but all superficial reflexes were present. The power of facial movement was good, but the movement of the lower part was better than that of the upper part.

The patient was seen again on September 11. He did not exhibit any residual signs of his previous illness. All sensory, motor and reflex phenomena were normal and the patient was discharged cured.

COMMENT

All of the cases of polyneuritis reported presented the quadriplegic manifestations, but they varied in the nature of cerebral nerve involvement. These patients variously had an involvement of the second, third, sixth, seventh, eighth, ninth, eleventh and twelfth nerves. Our patient had bilateral involvement of the seventh nerve. In all of the cases reported, the motor phenomena of the patient predominated, with the sensory symptoms and signs playing a minor part. This type of polyneuritis is usually of infectious origin, and the picture closely resembles that occurring as a complication of diphtheria, influenza, typhoid fever, measles, scarlet fever, whooping cough, gonorrhea and syphilis. Toxic polyneuritis, resulting from alcohol, lead, arsenic, coal tars, mercury and other metals, also resembles this picture.¹⁰

The common characteristics of all of the patients with parotitic quadriplegia were flaccid paralysis of all the extremities, loss of both deep and superficial reflexes, slight or no superficial sensory disorders and a disturbance of the deep senses such as the joint and vibratory senses.

None of the cases were fatal. All of the patients recovered completely, although the duration of the illness varied from one month to one year.

The meningitis, however, which occurs with mumps is a much more frequent phenomenon. Acker¹ has collected 150 cases from the literature. Wollstein¹¹ states that meningitis or meningo-encephalitis occurs in 23 per cent of the cases of epidemic mumps. Gordon¹² reported four fatal cases of mumps meningitis, and at autopsy demonstrated a lymphocytic infiltration of the pia-arachnoid with flattening of the sulci as evidence of increased intracranial pressure. The spinal fluid in all cases of meningitis has always been clear and under pressure, and has contained a small number of lymphocytes (from 15 to 200) and a large amount of globulin.

10 Pollock, L. J. and Cecil, R. L. *Textbook of Medicine*. Philadelphia, W. B. Saunders Company, 1927, p. 1334.

11 Wollstein, M. (footnote 10, p. 288).

12 Gordon, M. H. *Lancet* 2: 275, 1913.

The question arises as to the exact localization of this lesion. With the absence of abdominal reflexes, the presence of meningeal signs, the few sensory manifestations and the predominatingly motor phenomena, one wonders whether in addition to the polyneuritis the patient did not have some involvement of the spinal cord. The loss of abdominal reflexes without a break in the peripheral portion of the arc, either motor or sensory, makes one suspicious that a central lesion was present. This case seems to confirm the growing concept among neuropathologists that in all cases of polyneuritis there are some minor changes in the cord.

SUMMARY

A unique case of polyneuritic quadriplegia and bilateral facial paralysis and meningitis complicating epidemic parotitis is reported.

EFFECT OF IODINE IN TOXIC ADENOMA^{*}

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In recent years there has developed a general belief that so-called adenomatous goiter with hyperthyroidism (toxic adenoma) and exophthalmic goiter are two separate diseases. Still more recently, this belief has been emphasized by the common acceptance of the view that iodine, though beneficial under certain conditions in exophthalmic goiter, is harmful to and contraindicated in cases of toxic adenoma. Such a difference in response to iodine might well be expected to occur were it true that a fundamental difference exists between these two types of thyrotoxicosis. However, conclusive evidence of such a difference has not been presented, and it seemed that further evidence concerning the nature of toxic adenoma would be obtained by a trial of the effect of iodine in such cases. Such a study could be expected to furnish further evidence of the relation existing between exophthalmic goiter and toxic adenoma. In 1924 we therefore began a study of the effect of iodine in cases of toxic adenoma.

METHODS

Unselected cases of toxic adenoma, in which treatment with iodine had not previously been used, were studied. The differential diagnosis in these cases was based on the generally accepted criteria for the diagnosis of toxic adenoma, namely, a characteristic history, the presence of a nodular goiter, absence of exophthalmos and absence of thrill and bruit over the thyroid gland. The average age of the patients in our series was 49 years, the average duration of symptoms was 28 years. Symptoms referable to the heart were a prominent feature in many of the cases. The pathologic observations were those of toxic adenoma in twenty-one of the twenty-five cases in which the examination was made. In the other four cases the presence of additional changes was at best questionable. The clinical material was obtained from a region of endemic goiter where such forms of the disease are common, and the diagnoses represent the combined opinion of several experienced observers. Special care was taken to exclude the so-called mixed forms of the disease, and a large number of such cases were discarded in this study.

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^{*}Read in abstract at the meeting of the American Society for Clinical Investigation, Atlantic City, May 2, 1927.

The plan of study called for a preliminary period of about ten days of rest in bed and ordinary medical treatment in the hospital for the purpose of diagnosis and stabilization. Iodine was then administered, nearly always in the form of a compound solution of iodine, 5 minims (0.3 cc), three times daily, and the effect noted. As a control, unselected cases of exophthalmic goiter in which the patients were similarly treated with iodine and a few cases of toxic adenoma in which the patients were not treated with iodine were observed.

RESULTS

Seventy-eight cases of toxic adenoma were available for study, and these patients were treated with iodine. For various reasons, chiefly social and economic, the complete plan of study could not be carried out in a considerable number of the cases, but fairly complete data was obtained in thirty of the seventy-eight. Less complete data was obtained

TABLE 1—*Percentage of Reduction of Basal Metabolic Rate to Normal in Thirty Unselected Cases of Toxic Adenoma in Which the Patients Were Treated With Iodine*

| Percentage of Reduction of Basal Metabolic Rate to Normal (+10) | Number of Cases |
|--|-----------------|
| Less than 25 | 6 |
| 25 to 49 | 9 |
| 50 to 74 | 8 |
| 75 to 100 | 7 |

in the remainder, and while these cases have not been used directly in this study, they offer important supplementary evidence in support of the observations obtained in the thirty cases more completely studied.

Twenty-four of the thirty patients, or 80 per cent, showed a favorable response to the iodine similar to that observed in unselected cases of exophthalmic goiter under similar conditions. In six cases, there was little or no response. Particularly important is the fact that evidence of an unfavorable effect of the iodine was obtained only when the administration of iodine was discontinued or unduly prolonged. In such instances, to be discussed later, a relapse occurred, as is seen in exophthalmic goiter under similar circumstances.

In charts 1, 2 and 3 are shown the curves of the basal metabolic rates in the twenty-four cases in which the patients' response to iodine was favorable. In table 1, the thirty cases are grouped according to the percentage of reduction of the basal metabolism to normal, for this purpose we used the last basal metabolic rate before the administration of iodine was begun¹ and the minimum rate after iodine (before opera-

1 When determinations of the basal metabolic rate were made on the day on which the administration of iodine was started or on the following day, they have been considered as the "pre-iodine" rate in this connection.

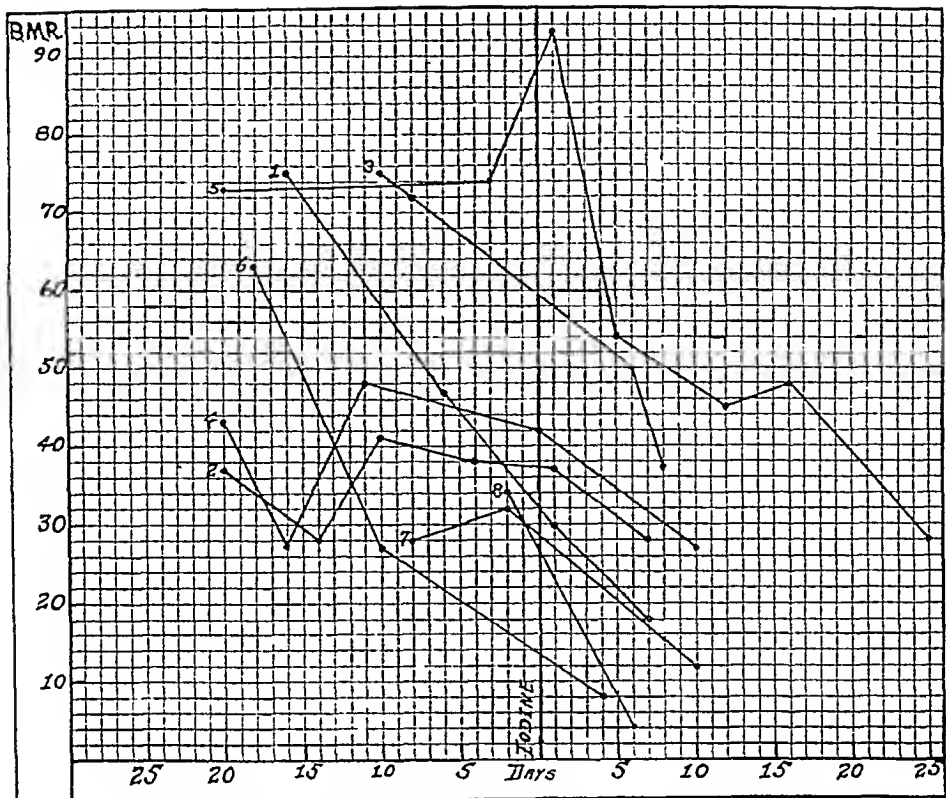


Chart 1—Curves of basal metabolic rate in cases of toxic adenoma, 1 to 8 inclusive, in which the patients were treated with iodine

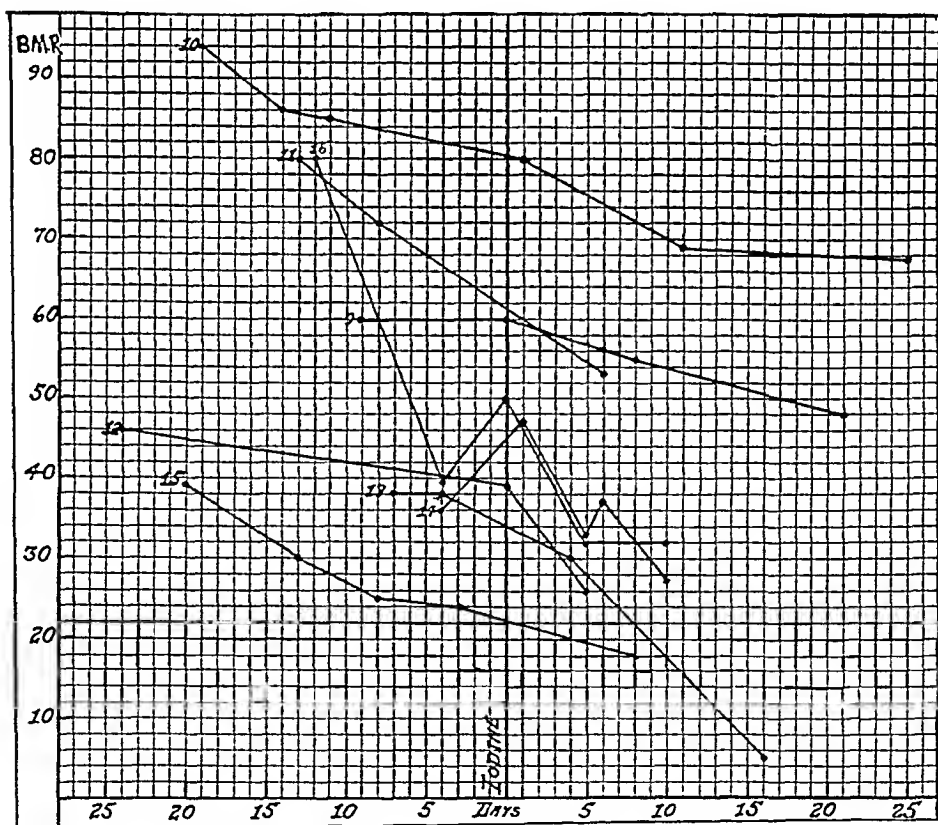


Chart 2—Curves of basal metabolic rate in cases of toxic adenoma, 9 to 16 inclusive, in which the patients were treated with iodine

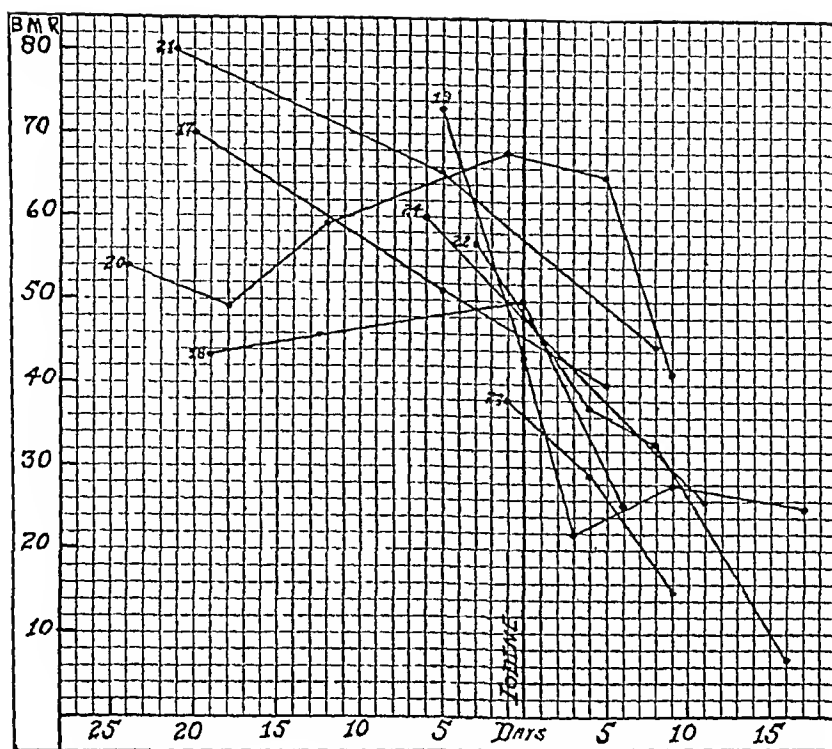


Chart 3—Curves of basal metabolic rate of cases of toxic adenoma, 17 to 24 inclusive, in which the patients were treated with iodine

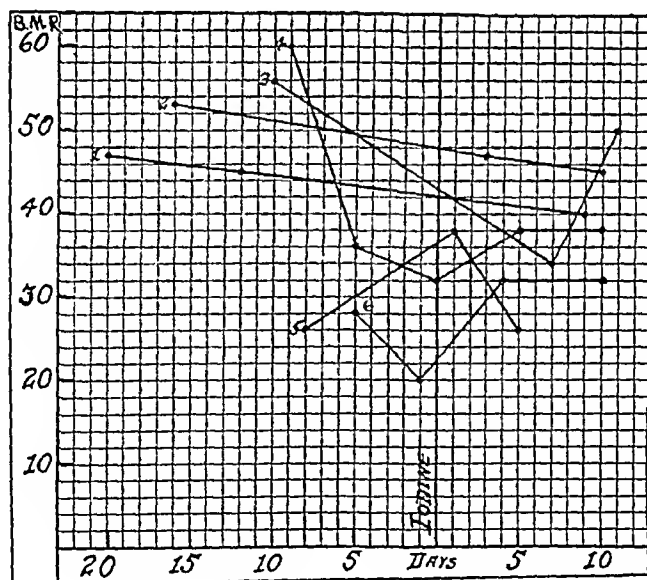


Chart 4—Curves of basal metabolic rate in six cases of toxic adenoma in which the patients showed little or no response to iodine

tion) It is seen that 6 of the 30 cases showed a reduction of less than 25 per cent, 9 showed a reduction of from 25 to 49 per cent, 8, a reduction of from 50 to 74 per cent, and 7, a reduction of from 75 to 100 per cent. Twenty-four showed a 25 per cent, or greater, reduction of the basal metabolic rate, and, with two exceptions, these cases have been included in the group showing a favorable response to iodine. The exceptions (cases 3 and 5, chart 4), although they showed a reduction in the basal metabolic rate of 50 and 42 per cent, respectively, have been included in the group showing no response to iodine, because clinical signs of improvement were absent. Conversely, two cases (cases 9 and 10, chart 2) that showed a reduction of the basal metabolic rate of less than 25 per cent have been included in the group showing a response to iodine, because there was marked remission of the clinical signs and symptoms of the disease. In this connection, it is important to

TABLE 2—*Comparison of Percentage of Reduction of Basal Metabolism in Twenty-Four Cases Each of Toxic Adenoma and Exophthalmic Goiter Showing Favorable Response to Iodine*

| Percentage of Reduction to Normal (+10) | Number of Cases | |
|--|-----------------|---------------------|
| | Toxic Adenoma | Exophthalmic Goiter |
| Less than 25 | 2 | 0 |
| 20 to 50 | 8 | 7 |
| 50 to 75 | 7 | 11 |
| 75 to 100 | 7 | 6 |

note that while the basal metabolism has been selected for the purposes of illustration as the best single evidence of the effect of iodine on these patients, it is not the only guide. In addition to the drop in basal metabolism, these patients exhibited a decreased pulse rate, gain in weight, lessened nervousness, amelioration of the cardiac symptoms and other clinical evidences of improvement.

In table 2 is shown a comparison of the degree of reduction of the basal metabolism in the twenty-four cases of toxic adenoma in which the patients showed the effect of iodine and in twenty-four unselected cases of exophthalmic goiter in which the patients showed the same favorable response to this drug. The average drop in the group of toxic adenoma was 22 points and in the exophthalmic group 30 points, while the average percentage of reduction of the basal metabolism was 58 and 64, respectively. Chart 5, in which are charted the last basal metabolic rates previous to the administration of iodine and the minimum rates after its administration, illustrates the similarity of response to iodine by patients with exophthalmic goiter and by those with toxic adenoma.

In four cases, there was a relapse or an escape from the effect of the iodine, and the previous or a worse clinical condition was noted. In two instances the relapse was associated with the discontinuance of

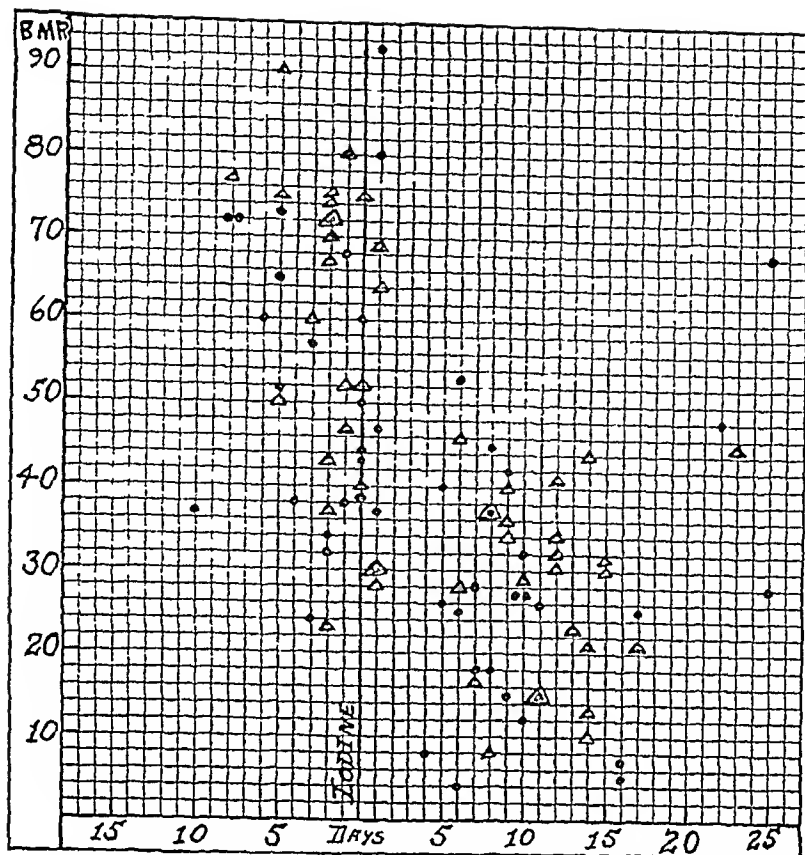


Chart 5—Comparison of basal metabolic rates before and after administration of iodine in twenty-four cases of toxic adenoma and in twenty-four cases of exophthalmic goiter. The last basal metabolic rate before the administration of iodine and the minimum rate after this medication are charted. The dots indicate cases of toxic adenoma, the triangles, exophthalmic goiter.

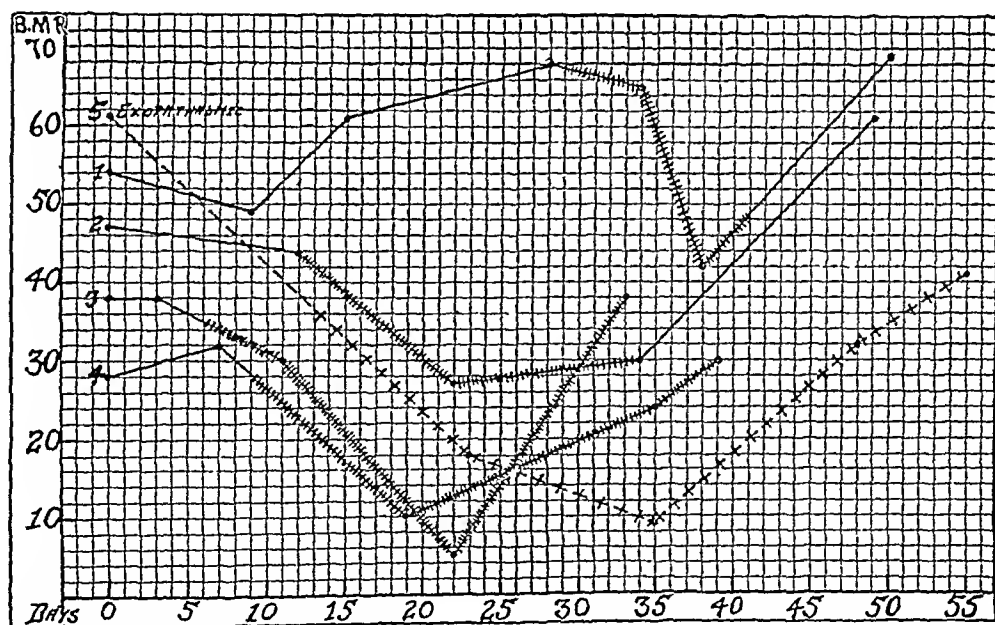


Chart 6—Curves of basal metabolic rate in four cases of toxic adenoma showing relapse following discontinuance or prolonged use of iodine (cases 1 and 2 and cases 3 and 4 respectively). A similar curve in a case of exophthalmic goiter is shown for comparison (case 5). Cross hatching indicates the period of iodine administration.

iodine, and in two cases with the long continued use of this drug. In all four cases the relapses followed initial remissions and were similar to those seen in cases of exophthalmic goiter under similar circumstances. Chart 6 shows the curves of the basal metabolic rates in these four cases, and for comparison a similar curve has been added in a case of exophthalmic goiter in which a relapse occurred following the prolonged use of iodine.

Patients with toxic adenoma not treated with iodine did not show the characteristic sudden drop in the metabolic rate and remission in clinical signs and symptoms seen in the patients treated with iodine.

COMMENT

The results presented in this paper indicate that patients with toxic adenoma, previously untreated with iodine, respond to its use in essentially the same way as patients with exophthalmic goiter. It is true that the basal metabolic rates do not show the same uniformity of drop following the administration of iodine or, on the average, as marked a drop as in selected cases of exophthalmic goiter. However, it should be borne in mind that the cases of toxic adenoma reported here are an unselected group, and that the results compare favorably with those obtained in a similarly unselected group of patients with exophthalmic goiter observed concurrently. It is also probable that had an opportunity been given for further determinations following the use of iodine, many of the patients would have exhibited a further drop in the basal metabolism. The fact that many had improved so remarkably that it seemed unwise to delay further the operative treatment indicates the degree of improvement. Further, the fact that similar clinical observations were made in forty-eight additional cases adds strong supplemental evidence of the favorable effect of the iodine in toxic adenoma. It is possible that larger doses of iodine might have caused a greater response in some of the more toxic cases, particularly in those in which the basal metabolism was high. As, however, a uniform dose of compound solution of iodine, 5 minims (0.3 cc) three times a day, was employed to maintain standard conditions, this factor remains undetermined.

Not only was a similarity observed between toxic adenoma and exophthalmic goiter as far as the favorable response to iodine is concerned, but a similarity in the lack of response was likewise noted. A certain proportion of the patients with toxic adenoma failed to respond to iodine as do a certain number of patients with exophthalmic goiter. Finally, the patients with toxic adenoma showed the same kind of relapse when iodine was discontinued and the same escape from its effect when the drug was long continued as was seen in the exophthalmic form of the disease. It would seem justifiable to conclude that whatever difference exists in the patient's response to treatment with iodine in toxic

adenoma and in exophthalmic goiter, it is merely a quantitative and not a qualitative one. Apparently, no essential difference in the pathogenesis of these two types of thyrotoxicosis can be assumed on the basis of the patient's response to treatment with iodine.

Occasional cases of toxic adenoma in which the patient responded favorably to iodine were reported in earlier articles on the action of iodine in exophthalmic goiter,² Boothby³ has stated that certain patients with hyperfunctioning adenomatous goiter improve after the administration of this drug. The explanation of the effect in such cases has generally been considered unsettled. Since this work was begun, however, two reports⁴ have appeared in which the observations are essentially in accord with ours, as are the conclusions of the authors. In fact, the average degree of drop in the basal metabolism in the cases reported by Starr in magnitude approaches even more closely that seen in exophthalmic goiter.

This response by patients with toxic adenoma to treatment with iodine, so essentially similar to that seen in exophthalmic goiter, cannot be explained on the basis of incorrect diagnosis, granting for the present that an acceptable differential diagnosis uniformly exists. All of our patients presented the clinical criteria said to be necessary for the diagnosis of toxic adenoma. They came from a region in which this condition is common, and were seen in a clinic in which the staff was familiar with this form of the disease. The pathologic observations were those commonly accepted as being characteristic of toxic adenoma, granting that such a pathologic differentiation exists. Finally, the independent report of essentially similar results from three widely separated clinics makes the likelihood of error based on mistaken diagnosis extremely improbable.

Of course, spontaneous improvement occurs in patients with toxic adenoma, but it also occurs in patients with exophthalmic goiter, and this fact may have some influence on the results obtained in both forms of the disease.

The reason for the quantitative difference in the response of patients with these two forms of the disease to treatment with iodine is undetermined. That it bears a relation to possible quantitative differences in the pathologic changes in the thyroid gland seems probable. The

2 Mason, E. H. Iodine Therapy in Toxic Goiter. *Tr. A. Am. Phys.* **39** 174, 1924.

3 Boothby, W. M. The Use of Iodine in Exophthalmic Goiter, *Endocrinology* **8** 727 (Nov.) 1924.

4 Graham, A. and Cutler, E. C. Exophthalmic Goiter and Toxic Adenoma. Similarity of Response to Iodine, *Ann. Surg.* **84** 497 (Oct.) 1926.
Starr, Paul. The Course of Hyperthyroidism Under Iodine Medication, *Arch. Int. Med.* **39** 520 (April) 1927.

qualitative changes which undoubtedly occur may play no direct part in the response to treatment, except as they modify quantitatively the changes common to both forms of the disease. The reason for the lack of response to iodine in occasional cases of both forms of the disease is not clear, and this problem, which may have a bearing on pathogenesis, awaits solution.

That patients with toxic adenoma have a relapse associated with the discontinuance of iodine or its prolonged use, following initial improvement, is of great importance aside from the fact that in this way they behave like patients with exophthalmic goiter. It explains completely, it seems to us, the widespread misconception that iodine initiates toxicity in cases of adenomatous goiter that previously were not toxic. After initial and unrecognized improvement, patients in whom unrecognized and often mild thyrotoxicosis has existed prior to the administration of iodine develop an exacerbation of symptoms associated with the discontinuance or prolonged use of the iodine. The same phenomenon occurs in cases of exophthalmic goiter, and the emphasis which has been focused on its occurrence in adenomatous goiter, together with the mistaken interpretation that has been made, has served to increase generally the belief in a fundamental difference between these two types of the disease. In contrast with this mistaken interpretation of the action of iodine, Graham and Cutler⁴ have recently reported that they failed to produce toxicity by giving iodine to patients with adenomatous, previously nontoxic, goiter. On the basis of our present knowledge, it seems improbable that iodine ever causes toxicity in a patient with a nontoxic adenomatous goiter, no matter in what doses the drug is used.

SUMMARY AND CONCLUSIONS

The response to treatment with iodine in thirty unselected patients with toxic adenoma who were previously untreated with iodine was essentially the same as that seen in unselected cases of exophthalmic goiter. Whatever differences exist are apparently quantitative, not qualitative. No essential difference in the pathogenesis of toxic adenoma and exophthalmic goiter can be assumed to exist on the basis of this response to treatment with iodine.

CHRONIC ULCERATIVE COLITIS WITH REFERENCE TO A BACTERIAL ETIOLOGY

EXPERIMENTAL STUDIES ³

MOSES PAULSON, M D

BALTIMORE

Chronic ulcerative colitis is an involvement of the large intestine and is of unknown etiology. The disease usually begins in the rectum, sometimes at the mucocutaneous border of the anus, it may remain localized in the rectum or it may extend upward. Anatomically, the process is characterized by primarily involving the mucosa, the condition varying from edema and hyperemia with easy bleeding to milium abscesses with subsequent discrete, petechial ulcers and "pocklike" scarring ¹. In some instances, there is an extension to the other layers of the intestine, resulting in the narrowing of the lumen of the affected part by extensive fibrosis. Myocardial changes and metastatic involvement of joints may occur ². Clinically, this disease is characterized by diarrhea—continuous or intermittent—with blood, pus, mucus, emaciation, debility, progressive anemia and at times pyrexia.

From time to time numerous investigators in different, and sometimes widely divergent, fields have made varied attempts to ascertain the etiologic factor, at least in part, of this condition. Impressions may have been gained, but definite conclusions have never prevailed in the light of subsequent experience and investigation.

The damage caused by this disease, the poor prognosis and the unsatisfactory management and treatment have led to another study with a view to determining, if possible, a bacterial etiology.

Specifically, the purpose of this study was to isolate bacteria, not including colon bacilli, from the bases of ulcers and from the mucosa when ulcers were not present in cases of acute exacerbations of chronic ulcerative colitis, with a view to establishing the consistent presence and preponderance of a definite bacterium, also to study the results in

³ From the Department of Medicine, Gastro-Intestinal Clinic and from the Department of Pathology and Bacteriology of the Johns Hopkins Hospital and School of Medicine.

* Read before the Section on Gastro-Enterology and Proctology at the Seventy-Eighth Annual Session of the American Medical Association, Washington, D C, May 20, 1927.

1 Bue, L A. Chronic Ulcerative Colitis, J A M A 87 1271 (Oct 16) 1926.

2 Brown, T R. Some Observations on Chronic Ulcerative Colitis, Ann Clin Med 4:425 1925.

rabbits following the intravenous administration of organisms thus isolated and from other sources. Incidentally, a small comparative study was made of the flora of the human colon when normal and when the seat of ulcerative colitis.

Aerobic and anaerobic streptococci isolated from feces and from the mucosa of the sigmoid of apparently normal persons, anaerobic streptococci from cases of ulcerative colitis, as well as more organisms from sources other than the intestine, are being studied further and will be the subject of a subsequent report.

METHODS OF STUDY

Fourteen cases of acute exacerbations of chronic ulcerative colitis were studied. Each patient was given two enemas, one, during the early night preceding the day of examination, the other in the morning, one hour before the investigation. Immediately preceding the examination, the anus was cleansed with a preparation of green soap and water followed by a 1:1,000 solution of mercuric chloride. A sterile sigmoidoscope was then inserted. If any excreta—blood, mucus, pus, feces—were encountered in spite of these efforts, they were aspirated by means of a water suction pump, through a sterile aspirator inserted through the sigmoidoscope. Sterile swabs then cleansed that part of the involved intestine from which material was to be secured for bacteriologic study. Finally, specially prepared swabs³ were introduced into the sigmoidoscope, with these the bases of ulcers were explored, and when ulcers were not present, the hypereemic, edematous, easily bleeding, friable mucous membrane was scraped.

Two, three and sometimes four swabs were employed during each examination. Each swab was introduced into a warmed tube of Rosenow's dextrose brain broth immediately after use. These tubes were incubated at 37 C for from six to twenty-four hours, that is to say, at least one tube in each case was incubated for six hours, the others remained in the incubator for twenty-four hours.

From each tube smears were made and stained by Gram's method for the purpose of ascertaining, morphologically, the types of organisms present.

There was a deviation from this procedure in one instance. In this case, following the administration of enemas and an anal cleansing, a sterile rectal tube was inserted for a distance of 10 cm. A viscid, mucopurulent, sanguinous excretion was secured. A loopful of this mixed material was placed in each of several warmed tubes of dextrose brain broth, and incubated, subsequently, smears were made in the manner as already described.

The work of isolating the organisms was next performed. This was done by the blood agar plate method. The mediums employed and the procedure followed in this method were essentially the same as those described and used by Brown in his monograph on streptococci,⁴ with the following addition: plates were made from six as well as from twenty-four hour cultures.

3 A cotton swab is attached to a 13 inch iron wire applicator. This is enclosed within a glass tube 11 inches long, the purpose of the latter is to assist in preventing the swab from touching any other than the desired part.

4 Brown, J. Howard. The Use of Blood Agar for the Study of Streptococci, Monograph 9, Rockefeller Inst. M. Research, 1919, p. 6.

These plates were incubated over night. On the following morning, they were studied for colonies with beta and unquestioned alpha zones. The plates were then refrigerated for twenty-four hours, and at the end of that period studied again, especially for colonies with alpha and gamma zones, and the number of each variety was ascertained. The alpha, beta and gamma classification used was that described by Brown⁵. The isolated colony was inoculated into dextrose brain broth and after twenty-four hours into pancreatic digest bouillon. After twenty-four hours' incubation, cultures were made from the latter on blood agar slants for stock and to secure material for the ascertaining of encapsulation by the india ink method, sugar fermentation and bile solubility tests were then performed.

The bile solubility test was performed in the manner described in the "Medical War Manual no. 6, Laboratory Methods, U. S. Army". The india ink method of determining encapsulation was done by mixing a loopful of material from a heavy twenty-four hour blood agar slant growth with a loopful of india ink and covering the moist preparation with a coverslip. This was examined immediately thereafter for the presence of a light halo (capsule) about the organism.

The sugar fermentation tests were performed in the following manner. Pure cultures were inoculated into mediums for fermentation tests within ninety-six hours after isolation. The test mediums were inoculated from pure cultures in pancreatic digest broth, a sugar-free medium, in which the organism grew abundantly. Pancreatic digest broth was also used as the basic medium for the fermentation tests. The test substances were dextrose, maltose, lactose, saccharose, raffinose, inulin, mannite and salacin autoclaved in 10 per cent aqueous solution and then added aseptically to the broth so as to make about a 1 per cent solution of the test substance in the broth. Milk was also used as a test medium. Cultures in the test mediums were incubated five days and then tested for acid production by the addition of a couple of drops of brom cresol purple solution to each tube. In the tests in which the indicator showed a variation from the original purple to a definite yellow, the cultures were regarded as fermented.

Rabbits weighing about 1,600 Gm. were used in this study. Great care was taken in their selection, they came from good stock and had never been used in any other experimental study. During the period of observation prior to their use, which varied from four days to weeks, they never appeared ill, were free from diarrhea, and grew consistently on a ration consisting of hay, oats, lettuce, cabbage and sprouts.

Reference has been made already to the over night incubation of dextrose brain broth inoculated with the desired colonies secured from blood agar plates. Such cultures were intravenously injected into rabbits in varying dosages. In some instances, one dose was administered, in most cases, more than one dose was given. In second and subsequent injections, the cultures used on each occasion were twenty-four hour growths in dextrose brain broth of the desired organisms secured from blood agar slant stock cultures, the second and subsequent injections were administered in varying dosages at frequent but irregular intervals. A total amount of from 2 to 15 cc. was given. In two instances, mixed cultures were administered. These were originally fished from beta zoned colonies in blood agar plates and grown in dextrose brain broth for twenty-four hours. When subsequent doses were administered, the cultures were prepared from blood agar slant stock cultures as heretofore described. The organisms present in

5 Brown, J. Howard. The Use of Blood Agar for the Study of Streptococci, Monograph 9, Rockefeller Inst. M. Research, 1919, p. 8.

these mixed cultures were isolated and individually studied, they proved to be *Bacillus coli* and alpha zoned chain-forming streptococci. A total of from 15 to 6 cc was administered.

B. coli was isolated from ulcers in a case of amebic dysentery as well as from a normal sigmoid. *B. dysenteriae* (Flexner and Shiga), a beta hemolytic streptococcus from the uterus of a human being suffering with puerperal sepsis and alpha hemolytic streptococcus secured from my throat, as well as a dead culture of a beta hemolytic streptococcus from a case of scarlatina, were injected into rabbits and studied in the manner already described. Dosages varying from 0.01 to 10 cc were administered.

Autopsies were performed on all animals that died or were killed. All viscera were examined carefully, and cultures of heart blood were taken and studied. Lesions were sectioned and later examined microscopically.

OBSERVATIONS

The primary dextrose brain broth cultures, without exception, were mixed. Morphologically, whether it was a six or a twenty-four hour culture, there was nothing characteristic about it other than a lesser or greater growth. In each instance there was a preponderance of gram-positive organisms. Gram stained smears from primary dextrose brain broth showed diplococcal, short and sometimes somewhat long chained arrangements of what appeared to be, on the basis of morphology, streptococci, small clumps of cocci, and rods suggestive of *B. welchii*. Gram-negative bacilli were present in abundance.

It was soon learned that the morphologic picture of the original or primary dextrose brain broth was not helpful, on the contrary, it was misleading. An abundance of gram-positive bacteria were invariably in evidence in stained smears. Yet it was so difficult to isolate any bacilli other than gram-negative bacilli on blood agar plates that in each of six cases an additional sigmoidoscopic examination was required, and in three other cases two additional examinations were necessary for the securing of more material for further attempts at isolation.

Because of these difficulties in isolation, freshly prepared blood agar plates from three cases of ulcerative colitis were placed in anaerobe jars for forty-eight hours. Invariably, colonies with beta zones predominated, surface colonies and sometimes colonies with gamma zones were present. The beta zoned colonies showed diplococcal and chain formation arrangements of streptococci, the surface colonies showed gram-positive bacilli (*B. welchii*), and the gamma zones evidenced gram-negative bacilli which fermented lactose and produced gas (*B. coli* group). These were contrasted with plates grown aerobically. These aerobic plates in most instances were dominated by gram-negative bacilli.

A similar interesting situation arose when material was secured from the mucosa of the sigmoids of three persons who had always been free, as far as could be ascertained from diarrhea and organic disease of the

gastro-intestinal tract. These persons were prepared for examination, and the material was secured from them in exactly the same manner as in cases of ulcerative colitis. In these apparently normal persons, streptococci were not demonstrable on aerobic blood agar plates, although stained smears from dextrose brain broth showed many gram-positive diplococci and chains of streptococci not unlike those seen in cases of

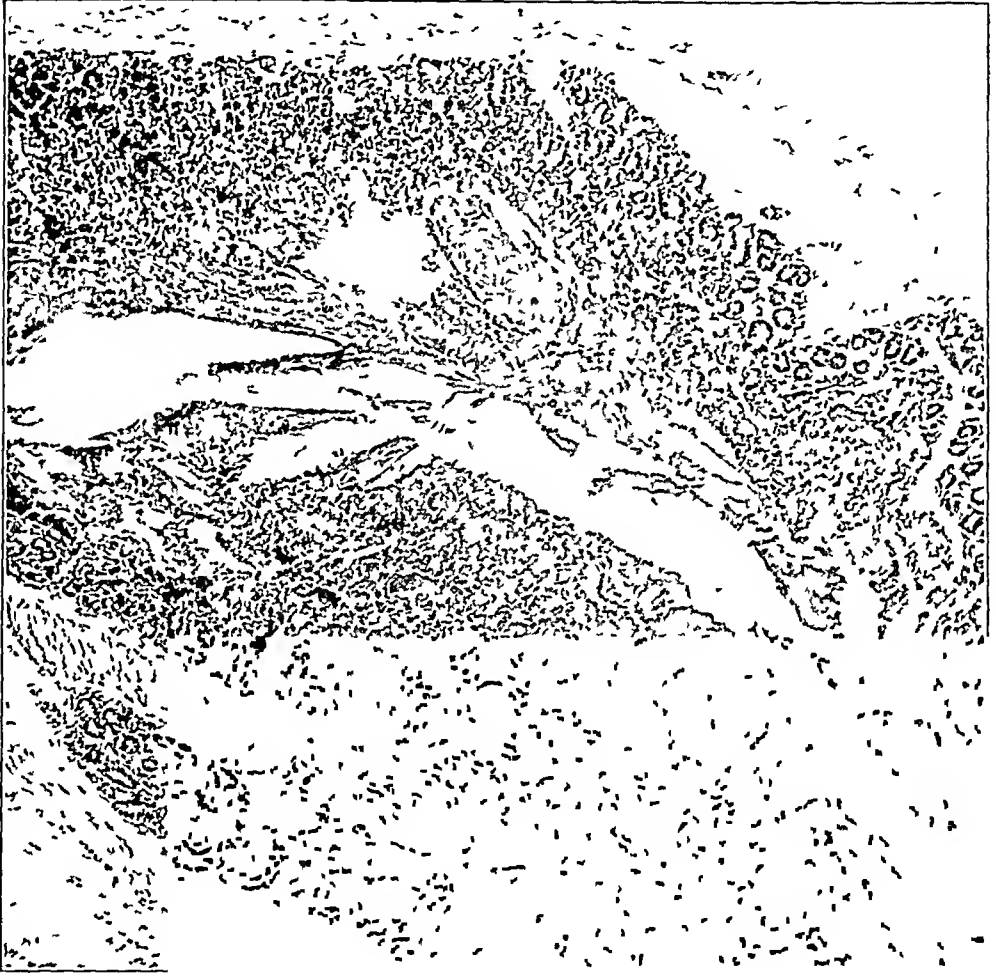


Fig. 1—Colon of rabbit intravenously injected with a culture of streptococci from an alpha zoned colony. The organism did not ferment saccharose, raffinose and inulin. There is some infiltration and, in part, necrosis of mucosa with submucous inflammatory involvement. The lens used in the illustrations was Zeiss, apochromate no. 10.

ulcerative colitis. Here, too, aerobically, surface, gamma and sometimes beta zoned deep colonies prevailed which proved to be gram-negative bacilli. Yet, when plates were placed in anaerobe jars for forty-eight hours, colonies similar to those noted on the plates grown anaerobically from cases of ulcerative colitis were present, except that in the latter group of cases, possibly more surface colonies of gram-positive bacilli (*B. welchii*) were found.

No alpha zoned colonies were noted on the plates incubated anaerobically with material either from apparently normal persons or from persons with ulcerative colitis. Brown however, points out that "under anaerobic conditions alpha type streptococci and pneumococci produce beta zones"⁶

In other words, other than an apparent increase in *B. welchii* on anaerobic plates and the presence of streptococci in aerobic plates in cases

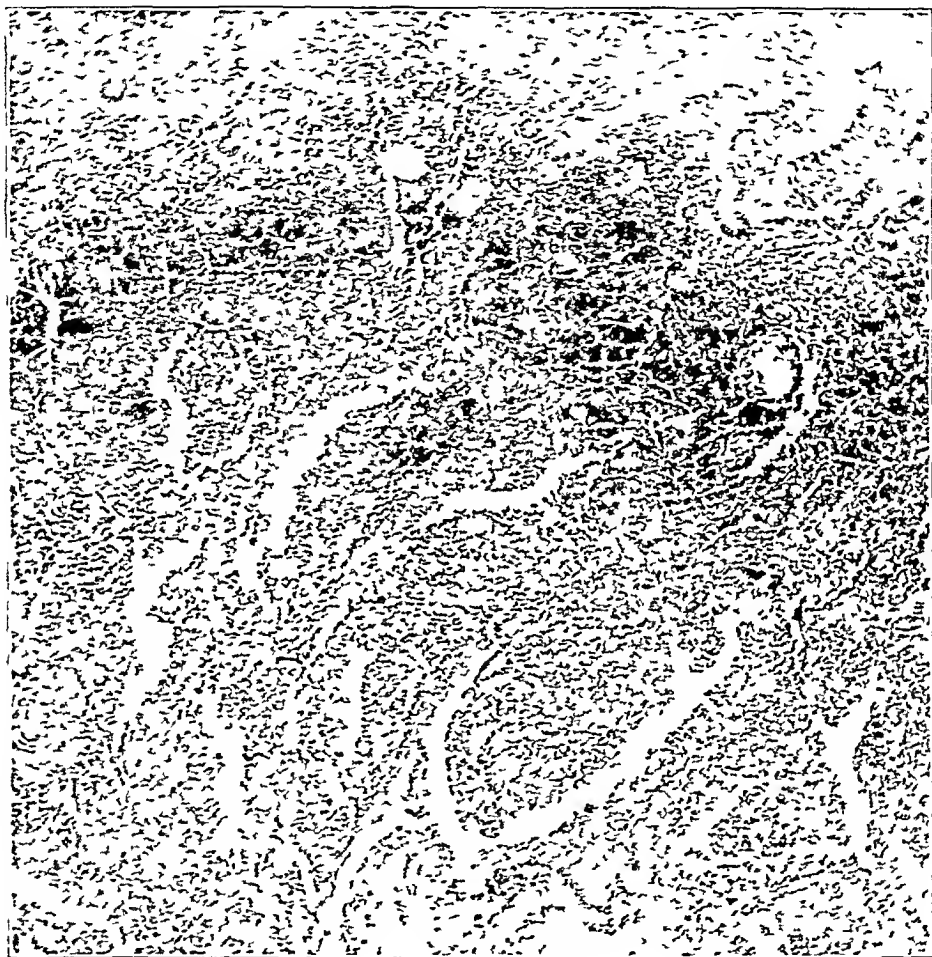


Fig 2—Rectum of rabbit intravenously injected with an alpha zoned streptococcus, diplococcal in morphology, and not fermenting inulin and mannite (Bargen's criteria). There is marked infiltration of submucosa.

of ulcerative colitis as contrasted with no demonstrable streptococci on aerobic plates from swabs from the thoroughly cleaned rectums and sigmoids of persons who did not present diarrhea or organic gastrointestinal disease. definite differences were not noted in this small com-

⁶ Brown J. Howard. The Use of Blood Agar for the Study of Streptococci. Monograph 9. Rockefeller Inst. M. Research. 1919. p. 95.

parative group Stained smears of primary dextrose brain broth cultures in this same small comparative group did not show any distinctive morphologic differences

Stained smears from fecal suspensions from pancreatic digest broth made from dejected excieta of three patients who had not had diarrhea or organic gastro-intestinal disease, but who had taken considerable milk in their diet, showed a morphologic picture not unlike that seen in primary dextrose brain broth cultures from material secured from the bases of ulcers in cases of acute exacerbations of chronic ulcerative colitis

Ten types of streptococci were isolated from thirteen cases (table 1) In the fourteenth, forms other than colon bacilli could not be isolated from three swabs which had been taken from the bases of ulcers on two separate occasions and after the examination of eighteen plates Eight types presented alpha zones, two, beta zoned colonies

To explain further In three cases, an alpha zoned colony predominated, but in only one of these three instances was the organism a diplococcus that did not ferment inulin and mannite (Bargen's criteria) Incidentally, in the other case in which the bacterium meeting Bargen's description was isolated, it did not appear in predominance In one case a beta hemolytic, chain-forming streptococcus was present in marked preponderance, in still another case, alpha and beta zoned colonies of chain-forming streptococci were about equally numerous and together represented only half of the total number of colonies present Two cases showed a preponderance of beta zoned colonies which proved to be mixed, i.e., gram-negative bacilli predominated over a chain-forming streptococcus Subsequent isolation resulted in the streptococci appearing as alpha zoned colonies on blood agar plates In the remaining seven cases, colon bacilli (gram-negative bacilli which fermented lactose and produced gas) dominated the scene, appearing in varied types of colony forms with few streptococci present

All of the cocci were insoluble in bile and did not show capsule formation No changes occurred in the retesting of the organisms by the fermentation test within from two to six months after the original isolation Variations did not occur in the morphologic pictures in liquid mediums after a similar period of time

The streptococci isolated from material secured from the bases of ulcers in cases of acute exacerbations of chronic ulcerative colitis as in streptococci isolated from other sources and other conditions, do not have any characteristic morphology within themselves It should be emphasized that the appearance of a lancet-shaped gram-positive diplococcus with little if any tendency to chain formation is not characteristic of any one type of streptococcus This appearance had been observed, not only in the group which had failed to ferment inulin and

TABLE 1—Results of Intravenous Injection of Rabbits with *Streptococci* from Cases of *Ulcerative Colitis*

| Organism | Type Colony | Did Not Ferment | Number of Rabbits Injected | Dose | Locations and Descriptions of Lesions | Diarrhea | | | |
|---|-------------|-------------------------------------|----------------------------|--|--|------------|----------|---------|----------|
| | | | | | | Clinically | | Autopsy | |
| | | | | | | Blood | No Blood | Blood | No Blood |
| Streptococci (very long chains) | Alpha | Sallein, raffinose, mannite, inulin | 12 | No 330, 1 dose, 5 cc | Colon hemorrhagic area 3 cm long, rectum ulceration, anorectal junction hemorrhagic and edematous, sections confirm | + | 0 | 0 | + |
| | | | | No 312, 4 doses, 15 cc | Pertoneum serosanguineous fluid, colon, rectum and anus entirely involved, lesions vary from hemorrhages to ulcers, sections confirm | 0 | + | + | 0 |
| | | | | No 311, 4 doses, 15 cc | Ileum submucous hemorrhages and ulcerations, sections show acute ulcers | 0 | 0 | + | 0 |
| | | | | No 354, 3 doses, 9 cc | Pertoneum serosanguineous fluid, duodenum ileum, rectum ulcerations, cecum hemorrhagic area, sections confirm | 0 | + | 0 | + |
| | | | | No 340, 2 doses, 6 cc | Colon and rectum ulcerations and submucous hemorrhages, sections confirm | + | 0 | + | 0 |
| | | | | Plus { No 344, 1 dose, 3 cc B coli { No 347, 5 doses, 15 cc | Laying hemorrhages, sections confirm | 0 | 0 | 0 | 0 |
| | | | | No 318, 1 dose, 2 cc | No lesions, animals died of septicemia | 0 | 0 | 0 | 0 |
| | | | | No 320, 1 dose, 5 cc | | 0 | 0 | 0 | 0 |
| | | | | No 328, 5 doses, 15 cc | | 0 | 0 | 0 | 0 |
| | | | | No 356, 4 doses, 15 cc | | 0 | 0 | 0 | 0 |
| Streptococci (diplococci in morphology) | Alpha | Inulin and mannite | 6 | No 348, 3 doses, 6½ cc | Laying hemorrhages, ulcerations in small intestine, sections confirm | 0 | 0 | 0 | 0 |
| | | | | No 318, 1 dose, 2 cc | No lesions, animals died of septicemia | 0 | 0 | 0 | 0 |
| | | | | No 320, 1 dose, 5 cc | | 0 | 0 | 0 | 0 |
| | | | | No 328, 5 doses, 15 cc | | 0 | 0 | 0 | 0 |
| | | | | No 356, 4 doses, 15 cc | | 0 | 0 | 0 | 0 |
| | | | | No 348, 3 doses, 6½ cc | Laying hemorrhages, ulcerations in small intestine, sections confirm | 0 | 0 | 0 | 0 |
| | | | | No 238, 3 doses, 14 cc | Colon injected, rectum ulcerated, sections show inflammation of mucosa in former, in latter submucosa involved | 0 | 0 | 0 | 0 |
| | | | | No 313, 4 doses, 15 cc | No lesions | 0 | 0 | 0 | 0 |
| | | | | No 315, 4 doses, 12 cc | | 0 | 0 | 0 | 0 |
| | | | | No 325, 4 doses, 15 cc | | 0 | 0 | 0 | 0 |
| | | | | No 305, 4 doses, 15 cc | | 0 | 0 | 0 | 0 |
| | | | | No 247, 2 doses, 8 cc | No lesions | 0 | 0 | 0 | 0 |

| | | | | | | | | | | |
|---|-------|---|---|--|--|---|-----|---|---|---------|
| Streptococci (morphologically— diplococci and short chains, later longer chains) | Alpha | Saccharose, raffinose, inulin | 4 | No 211, 3 doses, 12 cc No 74, 1 dose, 5 cc No 324, 1 dose, 5 cc No 229, 4 doses, 15 cc | Heart pericarditis with effusion, myocardial abscess, ileum submucous hemorrhage, colon and rectum submucous hemorrhages and ulcerations, sections confirm Colon submucous hemorrhages and ulcera tions, sections confirm No lesions Living | 0 | + | + | 0 | |
| Streptococci, (chain forma tion) plus B coli | Alpha | Lactose, milk acidified, saccha- rose, raffinose, inulin | 2 | No 345, 1 dose, 3 cc No 346, 1 dose, 3 cc | Gallbladder enlarged, cecum hemorrhagic area ulceration, sections confirm Cecum ulceration, colon and rectum ulcera tions, sections confirm | 0 | 0 | 0 | + | |
| Streptococci (diplococci) | Alpha | Mannite | 6 | No 361, 4 doses, 14 cc No 240, 1 dose, 8 cc No 257, 1 dose, 5 cc No 359, 5 doses, 15 cc } No 357, 5 doses, 15 cc } No 224, 2 doses, 12 cc } | Bronchopneumonia, colon incl rectum sub mucous hemorrhage and ulcerations, sections confirm Ileum hemorrhagic area, colon ulceration, gallbladder enlarged, sections show involve ment in mucosa and submucosa Colon hemorrhagic patch, sections show mu- cosal necrosis with inflammatory reaction in submucosa No lesions Living | + | (?) | 0 | + | (mucus) |
| Streptococci (few diplococci, chiefly short but later longer chains) | Alpha | Inulin | 2 | No 376, 6 doses, 30 cc } No 377, 6 doses, 30 cc } | No lesions | 0 | 0 | + | 0 | 0 |
| Streptococci (chain forming) | Beta | Inulin, man- nite, raffinose | 2 | No 383, 4 doses, 14 cc } No 349, 2 doses, 4 cc } | No lesions | 0 | 0 | 0 | 0 | 0 |

mannite (the same group had fermented all other test substances mentioned under 'Methods of Study') but in strains which fermented all but mannite. This morphology was similarly observed in a strain not fermenting inulin although it fermented mannite. In a six to twelve hour culture in liquid medium of a streptococcal strain not fermenting saccharose raffinose and inulin and in a similar culture of another strain not fermenting saccharose raffinose inulin and lactose but acidifying milk diplococci with virtually no tendency to chain formation were in



Fig 3—Rectum of rabbit injected intravenously with an alpha zoned, long chain forming streptococcus not fermenting salicin raffinose, mannite and inulin. There is marked inflammatory reaction in the submucosa with lymphoid hyperplasia.

evidence in stained smears. Only after subcultivation in liquid mediums for twenty-four hours did the last two mentioned types show definite short chain formation.

Blood agar plates showing alpha colonies after being refrigerated for about a month in some instances evidenced *grossly* beta zoned colonies but the microscopic examination revealed that the change was only apparent for the blood corpuscles about the colonies were still

present. Frequently, gamma colonies on blood agar plates—plates kept at room temperature for about a week or more—showed some alteration in the appearance of the surrounding medium. Microscopically, however, it was evident that the colonies were neither alpha nor beta. In a few cases, stock cultures some months old were replated. No changes from the original were observed in the type of colony appearing then on the blood agar plates. It is submitted that the constancy of the

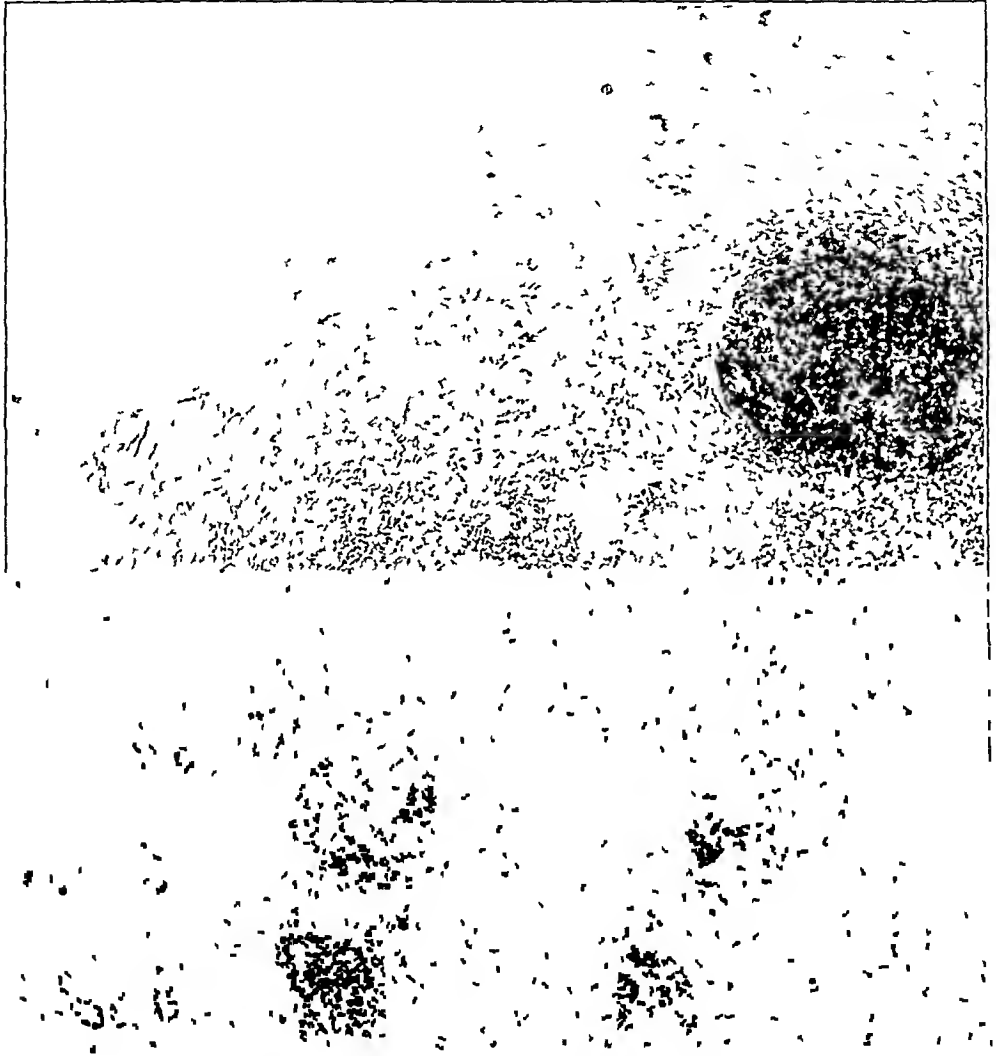


Fig 4—Rectum of rabbit injected intravenously with a culture from a beta zoned colony. The culture was mixed colon bacilli and an alpha zoned chain forming streptococcus. The latter organism did not ferment lactose, saccharose, raffinose, inulin and acidified milk. There is mucosal necrosis, marked cellular infiltration in the submucosa and lymphoid hyperplasia.

colonies on blood agar plates as seen by *microscopic* examination, as well as the constancy of the morphology and of the fermentation tests, modestly confirms the work of Brown.⁷

⁷ Brown, J. Howard. The Use of Blood Agar for the Study of Streptococci, Monograph 9, Rockefeller Inst. M. Research, 1919, pp. 77-82.

Thirty-four rabbits were injected intravenously with seven types of organisms isolated from cases of ulcerative colitis after the manner already described in detail (table 1). Four rabbits are living, they did not show diarrhea or signs of illness at any time, thirty died or were killed and fourteen showed lesions, confirmed by section, varying from mucosal to mucous and submucous inflammatory involvements, with the muscularis sometimes invaded. The lesions ranged from hemorrhages and necroses to ulcerations. The locations of the lesions were as fol-



Fig 5—Colon of rabbit injected intravenously with an alpha zoned streptococcus, diplococcal in morphology, which did not ferment mannite. The mucosa is destroyed. There is marked cellular infiltration in the submucosa.

lows: duodenum, 1, jejunum, 1, ileum, 5, appendix, 0, cecum, 3, colon, 10, rectum, 9, anus, 2.

Six of the thirty rabbits which came to autopsy were injected intravenously with a bacterium that met the following criteria. The organism presented itself on a blood agar plate as an alpha zoned colony, it appeared constantly as a diplococcus without tendency to chain formation, it did not ferment inulin and mannite, and, like all other organisms studied, it was insoluble in bile and did not present any capsules (Bargen's criteria). One rabbit of this group showed a lesion in the

colon and rectum, but did not give any evidence of diarrhea. The other five rabbits did not give any evidence of lesions or diarrhea. The remaining twenty-four rabbits were injected with other types of streptococci isolated from cases of ulcerative colitis. The lesions occurred exactly as already enumerated with reference to locations, with the exception of the one colon and one rectal lesion noted already. Eight of the twenty-four rabbits showed evidences of diarrhea about their bodies and cages, four showed blood and four did not. At autopsy, five rabbits showed loose, ill formed fecal material, in two of these the feces presented mucus, but blood was not seen in the feces of any of them, six rabbits showed evidences of diarrhea with blood. In all, twelve rabbits showed diarrhea in one way or another.

Twenty-two of the rabbits were injected intravenously with definite chain producing streptococci, ten showed lesions in the following locations: duodenum, 1, jejunum, 1, ileum, 4, appendix, 0, cecum, 3, colon, 6, rectum, 7, anus, 2.

In none of the thirty rabbits on which autopsy was performed were gross demonstrable lesions noted elsewhere than in the intestine, with the exception of pericarditis with effusion and a myocardial abscess in one, bronchopneumonia in another, and an enlarged gallbladder in each of two others. These five gross extra-enteric lesions occurred among the fourteen animals showing intestinal involvements.

Sixteen of the thirty rabbits intravenously injected with various forms of streptococci from cases of ulcerative colitis did not manifest any lesions at autopsy. They died from septicemia. The organisms injected were recovered from the heart blood.

Twenty additional rabbits were injected intravenously with seven types of bacteria from sources other than the bowel of patients with ulcerative colitis (table 2). Four rabbits are still living, and they did not show evidences of diarrhea or signs of illness at any time. Twelve of the sixteen rabbits that died or were killed showed lesions in the intestinal tract, confirmed by section. Grossly and microscopically, the lesions were not unlike those seen in rabbits injected with organisms from cases of ulcerative colitis, they varied from mucosal to mucous and submucous inflammatory involvements, with the muscularis sometimes invaded, the lesions ranged from hemorrhages to necroses or ulcerations. The locations of these involvements within the intestine, however, were different: duodenum, 0, jejunum, 1, ileum, 4, ileocecal valve, 1, appendix, 0, cecum, 6, colon, 4, rectum, 5, anus, 0. Two rabbits showed definite involvement of the gallbladder, one showed a definitely enlarged spleen and another, an hepatic abscess, otherwise no other viscera were grossly involved. In the few rabbits with extra-enteric lesions, the intestinal involvements were the more marked, pronounced or extensive, with the possible exception of the case of the hepatic abscess. Nine of the

TABLE 2—Results of the Intramuscular Injections of Rabbits with Organisms from Other Sources

| Organism | Source | Number of Rabbits Infected | Dose | Diarrhea | | | | Autopsy |
|---|------------------------------|----------------------------|-------------------------------------|---|----------|-------|----------|---------|
| | | | | Clinically | | Blood | | |
| | | | | Blood | No Blood | Blood | No Blood | |
| B dysenteriae (Shiga) | Bacillary dysentery | 1 | A, 1 dose, 2 cc | 0 | 0 | 0 | 0 | 0 |
| | | | No 32, 3 doses, 2 cc | 0 | 0 | 0 | 0 | 1 |
| | | | No 35, 5 doses, 1 cc | 1 | 0 | 1 | 0 | 0 |
| | | | Location and Description of Lesions | | | | | |
| B dysenteriae (Flexner) | Bacillary dysentery | 1 | No 36, 1 dose, 2 cc | Colon several hemorrhagic areas, section involve ment of mucosa | | | | |
| | | | No 38, 1 dose, 1 cc | Small intestine hemorrhagic fluid, cecum edema tous, hepatic abscess | | | | |
| | | | No 39, 1 dose, 2 cc | Gallbladder distended, cecum ulcerations, sections involvement of mucosa and submucosa in one, all layers in another | | | | |
| | | | No 38, 3 doses, 3/4 cc | Lesions in rectum? Not borne out by section | | | | |
| B coli | Amoebic dysentery | 1 | No 37, 1 dose, 3 cc | Cecum ulceration, confined by section | | | | |
| | | | No 38, 1 dose, 5 cc | Hemorrhagic fluid in small intestine | | | | |
| | | | No 39, 1 dose, 5 cc | Laying | | | | |
| | | | No 39, 1 dose, 3 cc | Cecum submucous hemorrhages and ulcers, sections confirm above | | | | |
| B coli | Normal sigmoid | 1 | No D, 1 dose, 2 cc | Ileocecal valve submucous hemorrhage, sections of both show involvement of mucosa and submucosa | | | | |
| | | | No C, 2 doses, 6 cc | Terminal ileum hemorrhage and phlegmon ulcers, cecum, hemorrhagic area, sections confirm above | | | | |
| | | | | Ileum hemorrhagic mucoid fluid, descending colon and rectum submucous hemorrhages and ulcerations confirmed by sections | | | | |
| | | | | Rectal submucous hemorrhages, sections show mucosal necrosis | | | | |
| Streptococcus (alpha-zoned colony) | Normal throat | 2 | No E, 1 dose, 10 cc | No lesions | | | | |
| | | | No D, 1 dose, 15 cc | | | | | |
| Did not ferment sulfide, indolose, mannite, and inulin | | | | | | | | |
| Streptococcus (beta-zoned colony) | Human uterine purpura sepsis | 1 | No 35, 1 dose, 2 cc | Ileum hemorrhagic patches, colon and rectum seg | | | | |
| | | | No 36, 3 doses, 8 cc | Cecal ulcers, confirmed by section | | | | |
| | | | No 37, 7 doses, 15 cc | Cecum ulcerations, rectum ulcerations | | | | |
| | | | No 38, 10 doses, 1 cc | Jejunum and ileum hemorrhages | | | | |
| Streptococcus (beta-zoned, dead culture, strain 22 B V) | Throat, septicemia | 1 | No 37, 3 doses, 5 cc | Gallbladder enlarged, ileum ulcer, colon and rec | | | | |
| | | | No 38, 1 dose, 1 cc | tum ulcers, sections show mucosal necrosis with cellular infiltration in submucosa and muscularis | | | | |
| | | | No 39, 1 dose, 10 cc | Laying | | | | |
| | | | No 39, 1 dose, 10 cc | Laying | | | | |

sixteen rabbits evidenced diarrhea with or without blood either clinically or at autopsy. Clinically, four animals showed diarrhea without blood, two, with blood. At autopsy, seven showed liquid feces in the colon without blood, two, with blood. Four rabbits did not show lesions, but died as a result of septicemia.

* *

Bargen of the Mayo Clinic, working in Rosenow's laboratory, claims to have isolated a gram-positive diplococcus which he regards as the etiologic factor in idiopathic ulcerative colitis. He ascribes definite cultural characteristics to this organism which he is able to isolate, and which appears in preponderance in 80 per cent of his cases, it appears on a blood agar plate as an alpha zoned colony, forms groups of twos and fours, sometimes has a capsule, is bile-insoluble and does not ferment inulin and mannite but always ferments dextrose, maltose, lactose, saccharose, raffinose and salacin and acidifies milk. He adds, however,



Fig 6—Rectum of rabbit injected intravenously with an alpha zoned streptococcus, chain forming, isolated from the author's throat. This organism did not ferment salacin, raffinose, mannite and inulin. The dark areas indicate submucous hemorrhages.

that after weeks or months, the reactions of the last six sugars may vary,⁸ in other words, the nonfermentation of inulin and mannite by this organism is a constant character. The intravenous injection of rabbits and some dogs with dextrose brain broth cultures produced lesions varying from hemorrhages to ulcerations, primarily in the colon, in somewhat more than 30 per cent of the rabbits so treated.⁸ No gross demonstrable lesions are reported elsewhere.

Diplococcus is merely a descriptive morphologic term. Many strains of streptococci under certain conditions grow as diplococci indistinguishable from that described by Bargen. As noted under "Observations" in this paper, several other varieties of streptococci from cases of ulcerative colitis gave similar appearances, especially in early cultures. In agree-

8 Bargen, J. A., and Logan, A. H. Experimental Studies on the Etiology of Chronic Ulcerative Colitis. Suggestions for a More Rational Form of Treatment, Collected Papers of Mayo Clinic, 1925 no. 17, pp. 266-267.

ment with this opinion Torrey stated that Bargaen sent me two of his strains (BB and HS) and in my opinion there is nothing in their morphology which is distinctive. The same morphological type is common in the human intestine in the feces of bottle-fed infants and in such material from adults taking considerable milk in their diet. The enterococcus may average somewhat larger but there are no real distinctive morphological differences.

Although Bargaen reported his ability to isolate the diplococcus in 80 per cent of sixty-eight cases investigated he mentioned having studied only twenty strains.⁹ Presumably, the other strains were diagnosed on the basis of morphology only.

Diplococci morphologically and culturally similar to those described by Bargaen are found not only in cases of ulcerative colitis but in other

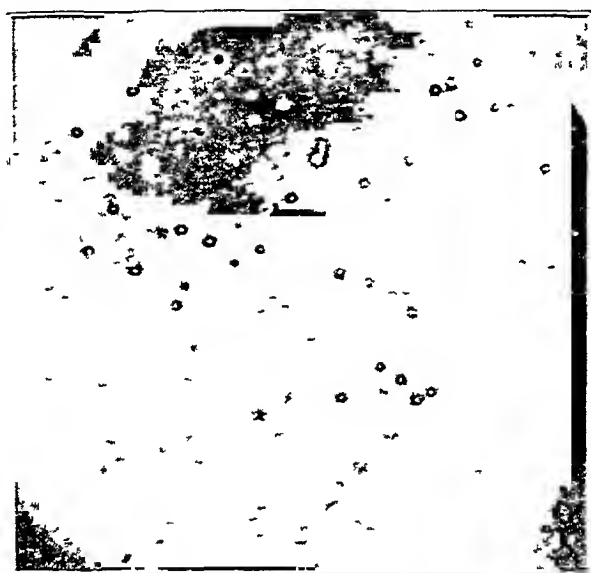


Fig. 7—Blood agar plate showing pure culture of alpha zoned colonies. Viewed through a lens the red blood cells contiguous to the colonies could be noted (Brown).

cases. Torrey reported that he had isolated this organism from the feces of a patient with mild cecitis.⁷ Bargaen stated that this organism cannot be isolated from feces. Denny and Frobisher,¹⁰ working in this laboratory, have isolated similar cocci from the throats of four nephritic patients. These patients did not have diarrhea and never suffered with organic disease of the digestive tract as far as could be ascertained.

9 Torrey, J. C. Bacteriology of the Human Colon. In Particular Reference to Nonspecific Ulcerative Colitis. *Trans. Am. Gastro-Enterol. Ass.* 1927 in press. personal communication to the author.

10 Denny, E. R., and Frobisher, Martin J.—Personal communication to the author.

It will be conceded that the diplococcus described by Baigen, when intravenously injected into rabbits and dogs, will produce lesions and diarrhea such as he has described. In reading Baigen's articles, however, it is not always clear whether he has injected mixed or pure

TABLE 3—*Streptococci Isolated from Two Cases of Ulcerative Colitis not Intravenously Injected Into Rabbits*

| Colony | Comment |
|----------------------------------|---|
| Alpha zoned on blood agar plates | The organism did not ferment mannite, inulin, raffinose and lactose and acidified milk |
| Alpha zoned on blood agar plates | The organism did not ferment lactose, saccharose, raffinose and inulin and acidified milk |
| Beta zoned on blood agar plates | The organism did not ferment mannite, inulin, raffinose and lactose and acidified milk |



Fig 8—An alpha zoned colony from plate shown in figure 7, under low power. An area of hemolysis about colony is present, but closely adjoining the latter are red blood cells (Brown)

cultures. Since similar lesions can be produced with a number of different organisms, it can hardly be conceded that lesions produced by the injection of mixed cultures have a specific etiology. Furthermore, it does not appear in Baigen's communications that he performed any control experiments. He offers as controls the work of Rosenow and others, who working independently of Baigen on problems other than ulcerative colitis, have injected streptococci from other sources into lower animals. Apparently Baigen has not injected intravenously into lower animals, other forms or types of streptococci, in pure culture, isolated from the bowel of patients with ulcerative colitis in order to make a comparative study.

Isolation in pure culture of the diplococcus described by Bargaen from an abscess in a protruding bowel of a patient with ulcerative colitis on whom an ileostomy had been performed does not necessarily mean that the organism isolated is the etiologic factor in this disease, since it may have been secondary

N W Jones, of Portland, Ore, reported before the American Gastro-Enterological Association, on May 3, 1927, that in a small study in collaboration with Benson and Menne, he was able to confirm Bargaen's work. He permitted the author to copy the technic employed and to quote him. These investigators employed Rosenow's technic, they injected primary dextrose brain broth cultures intravenously into rabbits. These cultures contained the mixed intestinal flora from cases of ulcerative colitis. These results are subject to the criticism offered with reference to the injection of mixed cultures.

The vaccine filtrates used by Bargaen in the treatment in these cases were made from the original¹¹ or primary dextrose brain broth cultures, hence, patients were receiving mixed autogenous vaccine filtrates. If it is assumed that Bargaen's diplococcus in pure culture might be used in the making of filtrates or vaccines proper, the lack of abruptness in the cessation of symptoms and signs when they are used, their employment over a variable but fairly long period of time, the supplementing of vaccine therapy with many other usual forms of treatment, suggest that the favorable response to treatment reported by Bargaen is a nonspecific, foreign protein reaction in a disease which presents a variable course and the acute exacerbations of which appear to be self-limited.

COMMENT AND SUMMARY

Fourteen cases of acute exacerbations of chronic ulcerative colitis have been studied with reference to a bacterial etiology.

Ten distinct types of streptococci were isolated in these cases. No one type was present in more than three cases. Eight varieties appeared as alpha zoned colonies on blood agar plates, two, as beta.

Seven types of these streptococci were intravenously injected into thirty-four rabbits, five of which produced lesions in these animals. Of thirty that came to autopsy, fourteen showed lesions, confirmed by section, these were primarily in the colon and rectum. Twelve rabbits manifested definite diarrhea with or without blood or mucus, clinically or at autopsy. Extra-enteric lesions were grossly demonstrable in each of four rabbits presenting intestinal involvements, in two, however, the major lesions were intestinal.

11 Bargaen, J. A., and Logan, A. H. Experimental Studies on the Etiology of Chronic Ulcerative Colitis. Suggestions for a More Rational Form of Treatment, Collected Papers of Mayo Clinic, 1925, no. 17, p. 273.

Twenty other rabbits were injected intravenously with seven types of bacteria from sources other than the bowel in cases of ulcerative colitis. Of sixteen rabbits on which autopsy was performed, twelve showed lesions which grossly and microscopically were not unlike those seen in rabbits injected with organisms from cases of ulcerative colitis. However, the location of the lesions was different, a lesser number occurring in the rectum and colon and a greater number elsewhere in the intestinal tract. There was one extra-enteric lesion in each of four rabbits, in three rabbits the major lesions were intestinal. Nine rabbits manifested diarrhea with or without blood or mucus, clinically or at autopsy.

The author believes that there was no difference between lesions produced in the intestines of rabbits by the intravenous injection of organisms isolated from cases of ulcerative colitis or from other sources. Grossly and microscopically, all lesions were similar, differing only as to their location within the intestinal tract.

It was interesting to note that in sections of lesions stained for bacteria, a variety of types of organisms were found which, morphologically, were analogous to the mixed intestinal flora of the rabbit, regardless of the type of organism intravenously injected into the animal.

There are no distinctive differences, morphologically, between primary dextrose brain broth cultures from material secured from the bases of cases of ulcerative colitis and those from swabs from cleansed normal sigmoids. Only in some instances did there seem to be an increase in gram-positive organisms in the former, but such a picture was not characteristic, stained smears of broth suspensions of dejected excreta from apparently normal persons taking considerable milk in their diet also presented a preponderance of gram-positive bacteria and appeared to be identical, in morphology, to stained smears from the primary cultures of cases of ulcerative colitis.

In a comparative study of the bacterial flora of a small group of normal persons and of cases with ulcerative colitis, *B. coli*, *B. welchii* and streptococci preponderated in the latter type of cases. One cannot say, as a result of this study, what definite rôle the two former organisms play in the causation of this disease. The appearance of streptococci in predominance may mean one of two things: either they were able to escape the cleansing enemas and swabbing by hiding in the ulcers where they multiplied because of an environment favorable to their growth, or their increased presence may indicate that they may be in some measure etiologically responsible for this condition.

In view of the author's study, it is felt that Baigen has established that the streptococcus or diplococcus described by him, an organism

that morphologically is not characteristic of any one type of gram-positive coccus inhabiting the normal or diseased human intestine, can be isolated with some degree of frequency in cases of ulcerative colitis, and that when this diplococcus is injected into animals, lesions in the colon and rectum are produced. Bargaen has not performed control experiments to establish specificity. His vaccine therapy appears to be non-specific.

Finally, in view of the fact that ten varieties of streptococci were found in fourteen cases of ulcerative colitis, that similar lesions were produced and chiefly produced in the colon and rectum of rabbits intravenously injected with any one of five types, and that in other rabbits intravenously injected with other organisms from other sources similar lesions were produced in the colon and rectum, I submit the statement that the bacterial etiology of ulcerative colitis is still undetermined.

The Johns Hopkins Hospital

ABSTRACT OF DISCUSSION

DR J HOWARD BROWN, Baltimore. It deserves to be emphasized that Dr Paulson's work is valuable because positive lesions were secured in animals. If a lesion had not been secured, it might well be said that failure to follow the technic which has been described by Dr Bargaen, who in turn followed Dr Rosenow, might be the cause of the failure to duplicate the results. At the beginning of this work, Dr Paulson was rather enthusiastic over the work which Dr Bargaen had done, and it was not with a view to discrediting that work that he undertook his experiments. At times while he was producing lesions he was inclined to believe that he was getting complete confirmation of Dr Bargaen's results, and it was only after he was urged to try other streptococci and to study their characteristics rather minutely that he took the attitude which he now has in regard to it.

In Dr Bargaen's work, there is, it seems, not a sufficient number of controls, that is, he points to the fact that in numerous rabbits injected with streptococci by other persons these lesions have not been described. However, it must be remembered that the mere statement that lesions were found in the appendix, in the heart or elsewhere, and that lesions were not found in other parts of the body cannot be taken as a control for work in which this particular lesion is being sought. I think Dr Bargaen's work suffers for lack of controls inoculated by himself with streptococci of other characteristics than that which he describes.

Dr Paulson emphasizes the fact that the streptococci found in these ulcers do not have a characteristic morphology, that is to say, the streptococci are very much like pneumococci in appearance, they are diplococci. Most streptococci grow as diplococci on the mucosa or on solid mediums and some of them in fluid mediums, so there is nothing particularly characteristic about that form. It is only after careful study of these streptococci in the blood agar plates and their fermentation reactions that they can be identified or differentiated one from another. There has been no appreciable variation in the cultural characters of these organisms since the time of their isolation. The fact that definite lesions were secured

indicates that more than one variety of streptococcus and possibly more than one other kind of organism can produce such lesions, so that ulcerative colitis can hardly be regarded as specific in the sense that it is produced by a single kind of streptococcus

DR FRANK SMITHIES, Chicago Were any nonbacterial proteins used intravenously, such as egg-white, peptone solutions and the like? Years ago, Vaughan and others showed the frequency with which such materials injected into the blood stream would produce lesions in the alimentary tract

DR A F R ANDRESEN, Brooklyn What Dr Smithies says suggests to me three cases which I have seen in the last six months that presented the characteristics of an ulcerative colitis, and which were apparently due to food allergy, in these cases, the condition cleared up promptly when the offending food proteins were eliminated from the diet. Their cultural characteristics varied in each case, and I think that in the study of chronic ulcerative colitis one has to be on the lookout constantly for that type of case

DR WALTER C ALVAREZ, Rochester, Minn The work of Dr Paulson shows the need for further study before it can be determined just what relation Bargaen's organism has to colitis. The problem is complicated by the fact that secondary invaders are commonly present in the lesions, in fact, Dr Buie, the proctologist at the Mayo Clinic, differentiates clearly between certain ulcers produced by the diplococcus and others nearby produced by or contaminated by secondary invaders. A point that has impressed me is that the diplococcus has been isolated in pure culture from pinpoint ulcerations found on the mucous membrane of the ileum, as it prolapsed through an ileostomy wound. I feel that doubts expressed about the specificity of this organism should not make one lose sight of the fact that Dr Logan, who for years made a particular study of this type of colitis and felt almost hopeless about curing it, now believes with Dr Bargaen that with the help of the vaccine filtrate it can frequently be either cured or certainly well arrested. I have seen some of the patients return after a year, fat and healthy, without ulcers and with haustra returning, and I think much has been achieved

DR MOSES PAULSON In answer to Dr Smithies' question, I can say that the injection of foreign proteins was suggested by Dr J Howard Brown on several occasions, but I never reached that point in this research for there was always so much to do. I am continuing with the problem, and I plan to inject into rabbits foreign proteins to see what lesions will occur in these animals, by way of comparison. However, I virtually did this when a dead culture of streptococci isolated from a case of scarlatina was injected into a rabbit, and lesions were secured, as detailed in the paper. With reference to Dr Alvarez's point that Dr Bargaen was able to demonstrate in the original or primary culture a pure culture of the diplococcus or streptococcus described by him (Bargaen) from an abscess in a protruding intestinal loop resulting from an ileostomy, this does not prove anything, for, as I have already mentioned in my paper, this organism may be purely secondary. It reminds me of the recent experience of Dr Small of the Philadelphia General Hospital. He isolated from the blood stream in patients with rheumatic fever a type of streptococcus that he felt was the causative factor, because when he injected the organism intravenously into rabbits, he obtained characteristic pathologic processes of the joints and heart only to be told in a "Current Comment" of *The Journal of the American Medical Association* that similar lesions have been obtained in lower animals by the injection of other forms of streptococci isolated from patients with rheumatic fever

Bargen deserves much credit for stimulating interest in this work. His experience with his vaccine in 385 cases reported at the last meeting (May 3, 1927) of the American Gastro-Enterological Association is interesting, but the good results he reports cannot be accepted as specific. My reasons, briefly, are first, as proved in this research, the specific organism of ulcerative colitis is yet to be discovered, second, Bargen made his vaccine filtrate from original or primary cultures, and therefore he was using a mixed vaccine or vaccine filtrate, third, his good results were obtained after varying but long periods in a disease which has natural remissions, and fourth, his patients received treatment in addition to the use of his vaccine therapy.

LOGARITHMIC TABLES FOR COMPUTING THE SURFACE AREA OF THE BODY ACCORDING TO DUBOIS' FORMULA

C H McCLOY
NEW YORK

In 1916, Dubois and Dubois¹ published a formula for the computation of the surface area of the body and presented a chart from which one could read the approximate surface area from the coordinates of height and weight if given in metric units. This chart permitted one to read the surface area to within approximately 150 square centimeters.

Boothby and Sandiford² and Feldman and Umanski publish nomograms for computing the surface area. In my experience, these have given large errors for the larger surface areas. These errors would be of small significance in ordinary clinical work, but they introduce an element of uncertainty in research work of any degree of refinement.

Owing to the use of surface area in the computation of normal vital capacity and in research in the field of basal metabolism, a means of ascertaining surface area quickly and accurately from either English or metric units of measurement is desirable. For those working extensively in this field, it would probably be an economy of time to prepare large charts on fine coordinate paper, like the smaller chart of Dubois and Dubois¹. For physicians and health workers who may desire from time to time to compute the surface area accurately and rapidly, I have prepared the following tables of logarithms. These will give the surface area to within 10 square centimeters, and, when one is acquainted with their use, they may be used rapidly.

The formula of Dubois and Dubois for the computation of the surface area is as follows:

$H^{.725} \times W^{.425} \times 71.84 = \text{surface area in square centimeters}$, in which H is height in centimeters, and W is weight in kilograms. It is obvious that the logarithm of the surface area (S A) computed from metric measurements may be found from the following:

$$\text{Log S A} = 0.725 (\text{Log Height}) + 0.425 (\text{Log Weight}) + \text{Log } 71.84$$

¹ From the Department of Physical Education, National Council, Y. M. C. A.

1 Dubois and Dubois. Clinical calorimetry, Arch. Int. Med. **17**: 863 (June) 1916.

2 Boothby and Sandiford. Boston Medical and Surgical Journal **185**: 337, 1921.

3 Feldman and Umanski. Lancet **1**: 273, 1922.

For English units of measurement, the logarithm of surface area (surface area being in square centimeters, but height and weight being in inches and pounds) would be as follows

$$0.725 \left(\text{Log } \frac{\text{Height in inches}}{0.3937} \right) + 0.425 \left(\text{Log } \frac{\text{Weight in pounds}}{2.20462} \right) + \log 71.84$$

Either of these processes is too involved for convenience. In the tables given below, this work has been condensed.

Table 1 gives the logarithm of (height in centimeters)⁷²⁵, table 2 gives the logarithm of ([weight in kilograms]⁴²⁵ × 71.84), table 3 gives the logarithm of $\left(\frac{\text{height in inches}}{39.37} \right)^{725}$, table 4 gives the logarithm of $\left[\left(\frac{\text{weight in pounds}}{2.20462} \right)^{425} \times 71.84 \right]$ table 5 gives the antilogarithms for all resultant logarithms needed for the computation of surface area. To use these tables, the logarithm corresponding to the height of the individual should be added to the logarithm corresponding to his weight. In table 5 will be found the surface area.

EXAMPLES

Metric Units—If height is 168 cm and weight is 61 Kg, tables 1 and 2 are used

| | |
|--------------|--------------|
| 168 cm = Log | 1 613 |
| 61 Kg = Log | 2 615 |
| Sum = | <u>4 228</u> |

In table 5, the antilogarithm of the logarithm 4 228 is 16,900, which is the surface area in square centimeters.

English Units—If the height is 64 inches and the weight 104 lb, tables 3 and 4 are used

| | |
|------------------|--------------|
| 64 inches = Log | 1 603 |
| 104 pounds = Log | 2 568 |
| Sum = | <u>4 171</u> |

In table 5 the antilogarithm of the logarithm 4 171 is 14,830, which is the surface area in square centimeters.

TABLE 1—*Logarithms of Height in Centimeters*

| Log (Height) ^{0.725} (Metric) | | | | | | | | | | | |
|--|-------|-----|-------|-----|-------|-----|-------|-----|-------|-----|-------|
| Cm | Log | Cm | Log | Cm | Log | Cm | Log | Cm | Log | Cm | Log |
| 100 | 1.450 | 120 | 1.507 | 140 | 1.556 | 160 | 1.598 | 180 | 1.635 | 200 | 1.638 |
| 102 | 1.456 | 122 | 1.512 | 142 | 1.560 | 162 | 1.602 | 182 | 1.639 | | |
| 104 | 1.462 | 124 | 1.518 | 144 | 1.565 | 164 | 1.606 | 184 | 1.642 | | |
| 106 | 1.468 | 126 | 1.523 | 146 | 1.569 | 166 | 1.610 | 186 | 1.645 | | |
| 108 | 1.474 | 128 | 1.528 | 148 | 1.573 | 168 | 1.613 | 188 | 1.649 | | |
| 110 | 1.480 | 130 | 1.533 | 150 | 1.577 | 170 | 1.617 | 190 | 1.652 | | |
| 112 | 1.486 | 132 | 1.537 | 152 | 1.582 | 172 | 1.612 | 192 | 1.655 | | |
| 114 | 1.491 | 134 | 1.542 | 154 | 1.585 | 174 | 1.621 | 194 | 1.659 | | |
| 116 | 1.497 | 136 | 1.547 | 156 | 1.590 | 176 | 1.628 | 196 | 1.662 | | |
| 118 | 1.502 | 138 | 1.551 | 158 | 1.594 | 178 | 1.632 | 198 | 1.665 | | |

TABLE 2—*Logarithms of Weight in Kilograms*

| Log [(Weight) ^{0.425} × 71.84] | | | | | | | | | |
|---|-------|------|-------|------|-------|------|-------|------|-------|
| Kg | Log | Kg | Log | Kg | Log | Kg | Log | Kg | Log |
| 18 0 | 2 390 | 35 0 | 2 513 | 50 0 | 2 578 | 65 0 | 2 627 | 80 0 | 2 635 |
| 18 5 | 2 395 | 35 5 | 2 515 | 50 5 | 2 580 | 65 5 | 2 628 | 80 5 | 2 666 |
| 19 0 | 2 400 | 36 0 | 2 518 | 51 0 | 2 582 | 66 0 | 2 630 | 81 0 | 2 667 |
| 19 5 | 2 405 | 36 5 | 2 520 | 51 5 | 2 584 | 66 5 | 2 631 | 81 5 | 2 670 |
| 20 0 | 2 409 | 37 0 | 2 523 | 52 0 | 2 586 | 67 0 | 2 632 | 82 0 | 2 670 |
| 20 5 | 2 414 | 37 5 | 2 525 | 52 5 | 2 587 | 67 5 | 2 633 | 82 5 | 2 671 |
| 21 0 | 2 418 | 38 0 | 2 528 | 53 0 | 2 589 | 68 0 | 2 635 | 83 0 | 2 672 |
| 21 5 | 2 423 | 38 5 | 2 530 | 53 5 | 2 591 | 68 5 | 2 637 | 83 5 | 2 673 |
| 22 0 | 2 427 | 39 0 | 2 533 | 54 0 | 2 593 | 69 0 | 2 638 | 84 0 | 2 674 |
| 22 5 | 2 431 | 39 5 | 2 535 | 54 5 | 2 594 | 69 5 | 2 639 | 84 5 | 2 675 |
| 23 0 | 2 435 | 40 0 | 2 537 | 55 0 | 2 596 | 70 0 | 2 641 | 85 0 | 2 676 |
| 23 5 | 2 439 | 40 5 | 2 540 | 55 5 | 2 598 | 70 5 | 2 642 | 85 5 | 2 677 |
| 24 0 | 2 443 | 41 0 | 2 542 | 56 0 | 2 599 | 71 0 | 2 643 | 86 0 | 2 679 |
| 24 5 | 2 447 | 41 5 | 2 544 | 56 5 | 2 601 | 71 5 | 2 644 | 86 5 | 2 680 |
| | | | | | | | | | |
| 25 0 | 2 450 | 42 0 | 2 546 | 57 0 | 2 603 | 72 0 | 2 646 | 87 0 | 2 681 |
| 25 5 | 2 454 | 42 5 | 2 548 | 57 5 | 2 604 | 72 5 | 2 647 | 87 5 | 2 682 |
| 26 0 | 2 458 | 43 0 | 2 551 | 58 0 | 2 606 | 73 0 | 2 648 | 88 0 | 2 683 |
| 26 5 | 2 461 | 43 5 | 2 553 | 58 5 | 2 607 | 73 5 | 2 650 | 88 5 | 2 684 |
| 27 0 | 2 465 | 44 0 | 2 555 | 59 0 | 2 609 | 74 0 | 2 651 | 89 0 | 2 685 |
| 27 5 | 2 468 | 44 5 | 2 557 | 59 5 | 2 611 | 74 5 | 2 652 | 89 5 | 2 686 |
| 28 0 | 2 471 | 45 0 | 2 559 | 60 0 | 2 612 | 75 0 | 2 653 | 90 0 | 2 687 |
| 28 5 | 2 475 | 45 5 | 2 561 | 60 5 | 2 614 | 75 5 | 2 654 | 90 5 | 2 688 |
| 29 0 | 2 478 | 46 0 | 2 563 | 61 0 | 2 615 | 76 0 | 2 656 | 91 0 | 2 689 |
| 29 5 | 2 481 | 46 5 | 2 565 | 61 5 | 2 617 | 76 5 | 2 657 | 91 5 | 2 690 |
| | | | | | | | | | |
| 30 0 | 2 484 | 47 0 | 2 567 | 62 0 | 2 618 | 77 0 | 2 658 | 92 0 | 2 691 |
| 30 5 | 2 487 | 47 5 | 2 569 | 62 5 | 2 620 | 77 5 | 2 659 | 92 5 | 2 692 |
| 31 0 | 2 490 | 48 0 | 2 571 | 63 0 | 2 621 | 78 0 | 2 661 | | |
| 31 5 | 2 493 | 48 5 | 2 573 | 63 5 | 2 623 | 78 5 | 2 662 | | |
| 32 0 | 2 496 | 49 0 | 2 575 | 64 0 | 2 624 | 79 0 | 2 663 | | |
| 32 5 | 2 499 | 49 5 | 2 577 | 64 5 | 2 625 | 79 5 | 2 664 | | |
| 33 0 | 2 502 | | | | | | | | |
| 33 5 | 2 504 | | | | | | | | |
| 34 0 | 2 507 | | | | | | | | |
| 34 5 | 2 510 | | | | | | | | |

TABLE 3—*Logarithms of Height in Inches*

| Log $\left(\frac{\text{Height}}{0.3937}\right)^{0.725}$ | | | | | | | |
|---|-------|--------|-------|--------|-------|--------|-------|
| Height | | | | | | | |
| Inches | Log | Inches | Log | Inches | Log | Inches | Log |
| 40 | 1 455 | 50 | 1 525 | 60 | 1 583 | 70 | 1 631 |
| 41 | 1 462 | 51 | 1 531 | 61 | 1 588 | 71 | 1 631 |
| 42 | 1 470 | 52 | 1 537 | 62 | 1 593 | 72 | 1 640 |
| 43 | 1 478 | 53 | 1 544 | 63 | 1 598 | 73 | 1 645 |
| 44 | 1 485 | 54 | 1 549 | 64 | 1 603 | 74 | 1 649 |
| | | | | | | | |
| 45 | 1 492 | 55 | 1 555 | 65 | 1 608 | 75 | 1 653 |
| 46 | 1 499 | 56 | 1 561 | 66 | 1 613 | 76 | 1 657 |
| 47 | 1 506 | 57 | 1 567 | 67 | 1 617 | 77 | 1 661 |
| 48 | 1 512 | 58 | 1 572 | 68 | 1 622 | 78 | 1 665 |
| 49 | 1 519 | 59 | 1 577 | 69 | 1 627 | 79 | 1 669 |

TABLE 4—*Logarithms of Weight in Pounds*

| Log $\left[\left(\frac{\text{Weight}}{2.20462} \right)^{0.425 \times 71.84} \right]$ | | | | | | | | | | | |
|--|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|
| Pounds | Log | Pounds | Log | Pounds | Log | Pounds | Log | Pounds | Log | Pounds | Log |
| 50 | 2.433 | 80 | 2.520 | 110 | 2.578 | 140 | 2.623 | 170 | 2.659 | 40 | 2.382 |
| 51 | 2.435 | 81 | 2.522 | 111 | 2.580 | 141 | 2.624 | 171 | 2.660 | 41 | 2.386 |
| 52 | 2.440 | 82 | 2.524 | 112 | 2.582 | 142 | 2.625 | 172 | 2.661 | 42 | 2.401 |
| 53 | 2.444 | 83 | 2.527 | 113 | 2.583 | 143 | 2.627 | 173 | 2.662 | 43 | 2.405 |
| 54 | 2.447 | 84 | 2.529 | 114 | 2.585 | 144 | 2.635 | 174 | 2.663 | 44 | 2.409 |
| 55 | 2.451 | 85 | 2.531 | 115 | 2.587 | 145 | 2.639 | 175 | 2.664 | 45 | 2.413 |
| 56 | 2.454 | 86 | 2.533 | 116 | 2.588 | 146 | 2.631 | 176 | 2.665 | 46 | 2.417 |
| 57 | 2.457 | 87 | 2.535 | 117 | 2.590 | 147 | 2.632 | 177 | 2.666 | 47 | 2.421 |
| 58 | 2.460 | 88 | 2.537 | 118 | 2.591 | 148 | 2.634 | 178 | 2.667 | 48 | 2.425 |
| 59 | 2.464 | 89 | 2.539 | 119 | 2.593 | 149 | 2.635 | 179 | 2.668 | 49 | 2.428 |
| 60 | 2.467 | 90 | 2.541 | 120 | 2.594 | 150 | 2.636 | 180 | 2.668 | | |
| 61 | 2.470 | 91 | 2.543 | 121 | 2.596 | 151 | 2.637 | 181 | 2.670 | | |
| 62 | 2.473 | 92 | 2.545 | 122 | 2.597 | 152 | 2.638 | 182 | 2.671 | | |
| 63 | 2.476 | 93 | 2.547 | 123 | 2.599 | 153 | 2.639 | 183 | 2.672 | | |
| 64 | 2.479 | 94 | 2.549 | 124 | 2.600 | 154 | 2.641 | 184 | 2.673 | | |
| 65 | 2.481 | 95 | 2.551 | 125 | 2.602 | 155 | 2.642 | 185 | 2.674 | | |
| 66 | 2.484 | 96 | 2.553 | 126 | 2.603 | 156 | 2.643 | 186 | 2.675 | | |
| 67 | 2.487 | 97 | 2.555 | 127 | 2.605 | 157 | 2.644 | 187 | 2.676 | | |
| 68 | 2.490 | 98 | 2.557 | 128 | 2.606 | 158 | 2.645 | 188 | 2.677 | | |
| 69 | 2.493 | 99 | 2.559 | 129 | 2.608 | 159 | 2.646 | 189 | 2.678 | | |
| 70 | 2.495 | 100 | 2.561 | 130 | 2.609 | 160 | 2.647 | 190 | 2.679 | | |
| 71 | 2.498 | 101 | 2.563 | 131 | 2.611 | 161 | 2.649 | 191 | 2.680 | | |
| 72 | 2.500 | 102 | 2.564 | 132 | 2.612 | 162 | 2.650 | 192 | 2.681 | | |
| 73 | 2.502 | 103 | 2.566 | 133 | 2.613 | 163 | 2.651 | 193 | 2.682 | | |
| 74 | 2.505 | 104 | 2.568 | 134 | 2.615 | 164 | 2.652 | 194 | 2.683 | | |
| 75 | 2.508 | | | 135 | 2.616 | 165 | 2.653 | 195 | 2.684 | | |
| 76 | 2.510 | 105 | 2.570 | 136 | 2.618 | 166 | 2.654 | 196 | 2.685 | | |
| 77 | 2.513 | 106 | 2.572 | 137 | 2.619 | 167 | 2.655 | 197 | 2.686 | | |
| 78 | 2.515 | 107 | 2.573 | 138 | 2.620 | 168 | 2.656 | 198 | 2.687 | | |
| 79 | 2.517 | 108 | 2.575 | 139 | 2.621 | 169 | 2.658 | 199 | 2.688 | | |
| | | 109 | 2.577 | | | | | 200 | 2.689 | | |

TABLE 5—*Anti-logarithms for Use in Computing Surface Area*

| Log | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|------|------|------|------|------|------|------|------|------|------|------|
| 3.84 | 6918 | 6934 | 6950 | 6966 | 6982 | 6998 | 7015 | 7031 | 7047 | 7063 |
| 3.85 | 7079 | 7096 | 7112 | 7129 | 7145 | 7161 | 7178 | 7194 | 7211 | 7228 |
| 3.86 | 7244 | 7261 | 7278 | 7295 | 7311 | 7328 | 7345 | 7362 | 7379 | 7396 |
| 3.87 | 7413 | 7430 | 7447 | 7464 | 7482 | 7499 | 7516 | 7534 | 7551 | 7568 |
| 3.88 | 7586 | 7603 | 7621 | 7638 | 7656 | 7674 | 7691 | 7709 | 7727 | 7745 |
| 3.89 | 7762 | 7780 | 7798 | 7816 | 7834 | 7852 | 7870 | 7889 | 7907 | 7925 |
| 3.90 | 7943 | 7962 | 7980 | 7998 | 8017 | 8035 | 8054 | 8072 | 8091 | 8110 |
| 3.91 | 8128 | 8147 | 8166 | 8185 | 8204 | 8222 | 8241 | 8260 | 8279 | 8299 |
| 3.92 | 8318 | 8337 | 8356 | 8375 | 8395 | 8414 | 8433 | 8453 | 8472 | 8492 |
| 3.93 | 8511 | 8531 | 8551 | 8570 | 8590 | 8610 | 8630 | 8650 | 8670 | 8690 |
| 3.94 | 8710 | 8730 | 8750 | 8770 | 8790 | 8810 | 8831 | 8851 | 8872 | 8892 |
| 3.95 | 8913 | 8933 | 8954 | 8974 | 8995 | 9016 | 9036 | 9057 | 9078 | 9099 |
| 3.96 | 9120 | 9141 | 9162 | 9183 | 9204 | 9226 | 9247 | 9268 | 9290 | 9311 |
| 3.97 | 9333 | 9354 | 9376 | 9397 | 9419 | 9441 | 9462 | 9484 | 9506 | 9528 |
| 3.98 | 9550 | 9572 | 9594 | 9616 | 9638 | 9661 | 9683 | 9705 | 9727 | 9750 |
| 3.99 | 9772 | 9795 | 9817 | 9840 | 9863 | 9886 | 9908 | 9931 | 9954 | 9977 |

TABLE 5—*Anti-logarithms for Use in Computing Surface Area—Continued*

| Log | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 4 00 | 10000 | 10020 | 10050 | 10070 | 10090 | 10120 | 10140 | 10160 | 10190 | 10210 |
| 4 01 | 10230 | 10260 | 10280 | 10300 | 10330 | 10350 | 10380 | 10400 | 10420 | 10450 |
| 4 02 | 10470 | 10500 | 10520 | 10540 | 10570 | 10590 | 10620 | 10640 | 10670 | 10690 |
| 4 03 | 10720 | 10740 | 10760 | 10790 | 10810 | 10840 | 10860 | 10890 | 10910 | 10940 |
| 4 04 | 10960 | 10990 | 11020 | 11040 | 11070 | 11090 | 11120 | 11140 | 11170 | 11190 |
| 4 05 | 11220 | 11250 | 11270 | 11300 | 11320 | 11350 | 11380 | 11400 | 11430 | 11460 |
| 4 06 | 11480 | 11510 | 11530 | 11560 | 11590 | 11610 | 11640 | 11670 | 11690 | 11720 |
| 4 07 | 11750 | 11780 | 11800 | 11830 | 11860 | 11890 | 11910 | 11940 | 11970 | 11990 |
| 4 08 | 12020 | 12050 | 12080 | 12110 | 12130 | 12160 | 12190 | 12220 | 12250 | 12270 |
| 4 09 | 12300 | 12330 | 12360 | 12390 | 12420 | 12450 | 12470 | 12500 | 12530 | 12560 |
| 4 10 | 12590 | 12620 | 12650 | 12680 | 12710 | 12740 | 12760 | 12790 | 12820 | 12850 |
| 4 11 | 12880 | 12910 | 12940 | 12970 | 13000 | 13030 | 13060 | 13090 | 13120 | 13150 |
| 4 12 | 13180 | 13210 | 13240 | 13270 | 13300 | 13340 | 13370 | 13400 | 13430 | 13460 |
| 4 13 | 13490 | 13520 | 13550 | 13580 | 13610 | 13650 | 13680 | 13710 | 13740 | 13770 |
| 4 14 | 13800 | 13840 | 13870 | 13900 | 13960 | 13960 | 14000 | 14030 | 14060 | 14090 |
| 4 15 | 14130 | 14160 | 14190 | 14220 | 14260 | 14290 | 14320 | 14350 | 14390 | 14420 |
| 4 16 | 14450 | 14490 | 14520 | 14550 | 14590 | 14620 | 14660 | 14690 | 14720 | 14760 |
| 4 17 | 14790 | 14830 | 14860 | 14890 | 14930 | 14960 | 15000 | 15030 | 15070 | 15100 |
| 4 18 | 15140 | 15170 | 15210 | 15240 | 15280 | 15310 | 15350 | 15380 | 15420 | 15450 |
| 4 19 | 15490 | 15520 | 15560 | 15600 | 15630 | 15670 | 15700 | 15740 | 15780 | 15810 |
| 4 20 | 15850 | 15890 | 15920 | 15960 | 16000 | 16030 | 16070 | 16110 | 16140 | 16180 |
| 4 21 | 16220 | 16260 | 16290 | 16330 | 16370 | 16410 | 16440 | 16480 | 16520 | 16560 |
| 4 22 | 16600 | 16630 | 16670 | 16710 | 16750 | 16790 | 16830 | 16870 | 16900 | 16940 |
| 4 23 | 16980 | 17020 | 17060 | 17100 | 17140 | 17180 | 17220 | 17260 | 17300 | 17340 |
| 4 24 | 17380 | 17420 | 17460 | 17500 | 17540 | 17580 | 17620 | 17660 | 17700 | 17740 |
| 4 25 | 17780 | 17820 | 17860 | 17910 | 17950 | 17990 | 18030 | 18070 | 18110 | 18160 |
| 4 26 | 18200 | 18240 | 18280 | 18320 | 18370 | 18410 | 18450 | 18490 | 18540 | 18580 |
| 4 27 | 18620 | 18660 | 18710 | 18750 | 18790 | 18840 | 18880 | 18920 | 18970 | 19010 |
| 4 28 | 19050 | 19100 | 19140 | 19190 | 19230 | 19280 | 19320 | 19360 | 19410 | 19450 |
| 4 29 | 19500 | 19540 | 19590 | 19630 | 19680 | 19720 | 19770 | 19820 | 19860 | 19910 |
| 4 30 | 19950 | 20000 | 20040 | 20090 | 20140 | 20180 | 20230 | 20280 | 20320 | 20370 |
| 4 31 | 20420 | 20460 | 20510 | 20560 | 20610 | 20650 | 20700 | 20750 | 20800 | 20840 |
| 4 32 | 20900 | 20940 | 20990 | 21040 | 21090 | 21130 | 21180 | 21230 | 21280 | 21330 |
| 4 33 | 21380 | 21430 | 21480 | 21530 | 21580 | 21630 | 21680 | 21730 | 21780 | 21830 |
| 4 34 | 21880 | 21930 | 21980 | 22030 | 22080 | 22130 | 22180 | 22230 | 22280 | 22340 |
| 4 35 | 22390 | 22440 | 22490 | 22540 | 22590 | 22650 | 22700 | 22750 | 22800 | 22860 |
| 4 36 | 22910 | 22960 | 23010 | 23070 | 23120 | 23170 | 23230 | 23280 | 23330 | 23390 |
| 4 37 | 23440 | 23500 | 23550 | 23600 | 23660 | 23710 | 23770 | 23820 | 23880 | 23930 |
| 4 38 | 23990 | 24040 | 24100 | 24150 | 24210 | 24270 | 24320 | 24380 | 24430 | 24490 |
| 4 39 | 24550 | 24600 | 24660 | 24720 | 24770 | 24830 | 24890 | 24950 | 25000 | 25060 |
| 4 40 | 25120 | 25180 | 25230 | 25290 | 25350 | 25410 | 25470 | 25530 | 25590 | 25640 |
| 4 41 | 25700 | 25760 | 25830 | 25880 | 25940 | 26000 | 26060 | 26120 | 26180 | 26240 |

THE INTRADERMAL SALT SOLUTION TEST IN NEPHRITIS IN ADULTS *

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AND
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In previous contributions from the Otho S A Sprague Memorial Institute, McClure and Aldrich ¹ reported work which demonstrated that the elevation ² made by intradermal injection of physiologic sodium chloride becomes impalpable more quickly in edematous and pre-edematous states than in the normal condition. Their reports dealt principally with edema associated with disturbances of the kidney in children, but also included several cases of cardiac disease and anemia.

Their studies of the edema with ³ associated renal disturbance led them to favor the hypothesis that the edema in the type of case described is due to an intoxication of the tissues which causes them to take up and to hold more water than normally. They found the test of considerable value in indicating the prognosis in these cases.

Subsequently Baker ³ used the test in the study of scarlet fever and diphtheria, and found it useful in indicating improvement or aggravation of these conditions.

Harrison ⁴ found a shortening of the time required for the disappearance of the wheal raised in the intradermal salt solution test in cases of lobar pneumonia in children, followed by a gradual return to normal after the crisis. Olmsted ⁵ applied the test to the study of

* From the Otho S A Sprague Memorial Institute and the Pathological Laboratory of the Cook County Hospital.

1 McClure, W B, and Aldrich, C A. Time Required for Disappearance of Intradermally Injected Salt Solution, J A M A **81** 293 (July 28) 1923.
McClure, W B, and Aldrich, C A. Intradermal Salt Solution Test, Its Prognostic Value in "Nephritis" with Generalized Edema, J A M A **82** 1425 (May 3) 1924.

2 In the test as described by McClure and Aldrich, 0.2 cc of a sterile 0.8 per cent aqueous solution of sodium chloride is injected intracutaneously under aseptic precautions in two places about 2 cm apart in the flexor surface of the forearm, and also usually either in the inner surface of the calf or the lateral aspect of the anterior surface of the leg. The time that the elevation remains palpable is noted. For normal children over 1 year of age, the time is one hour or longer. For white adults, the normal time seems to be somewhat higher than in children, and still higher in negro adults (Lash, A F. Surg Gynec Obst **43** 40, 1926).

3 Baker, W J. Intradermal Salt Solution Test in Scarlet Fever and Diphtheria Patients, J A M A **83** 1566 (Nov 15) 1924.

4 Harrison, J. Intradermal Salt Solution Test in Lobar Pneumonia in Children, J A M A **84** 1258 (April 25) 1925.

5 Olmsted, H C. Intradermal Salt Solution Test in Cardiac Disease in Children, Arch Int Med **37** 281 (Feb) 1926.

cardiac disease in children Cohen and his co-workers⁶ found a marked decrease in the time of the wheal disappearance in the extremities, in the presence of a vascular pathologic condition, and found the test useful in determining the level of adequate circulation in planning for surgical intervention Kunde⁷ extended the study of the test to a series of adult patients with different forms of nephritis, typhoid fever, toxemias of pregnancy and other conditions, and attempted to correlate the observations with regard to the time necessary for the disappearance of the wheal with the observations made with the elastometer and those made on the urine and on the blood Lash⁸ made use of this test in the study of the toxemias of pregnancy, and found a close relationship between the degree of severity of the toxemia and the amount of lowering of the disappearance time Guggenheimer and Hirsch⁹ studied edema with the aid of this test and obtained results similar to those of McClure and Aldrich and others They offer, however, a mechanical hypothesis to explain the rapid absorption of salt solution by edematous tissues

INTRADERMAL SALT SOLUTION TEST IN NEPHRITIS IN ADULTS

The study of the test in nephritis in adults is made difficult by the scarcity of uncomplicated cases, the uncertainty of the clinical determination of their type and the extent to which cardiac and vascular disturbances play a part in their symptoms

In our series of cases, with a clinical diagnosis of some form of nephritis, there were patients with and without edema

The basic observation of McClure and Aldrich that the elevation produced by the intradermal injection of physiologic sodium chloride solution disappears rapidly in edematous areas has been found to be true

A short disappearance time was also found in some cases in which there was no palpable edema, which was in accordance with the observations of McClure and Aldrich who had found the time shortened in edematous patients in areas of skin in which palpable edema was absent

The observations in the cases studied by us are summarized in the accompanying table

6 Cohen, M B Intracutaneous Salt Solution Test, Preliminary Report of Simple Method for Deficiency of Circulation in Extremities, *J A M A* **84** 1561 (May 23) 1925 Cohen, M B, Applebaum, H S, and Hainsworth, E L Intracutaneous Salt Solution Test, Its Use as Test of Efficiency of Circulation in Extremities, *J A M A* **86** 1677 (May 29) 1926 Cohen, M B, and Stern, W G Intracutaneous Salt Solution Wheal Test, Its Value in Disturbances of Circulation in Extremities, *J A M A* **87** 1355 (Oct 23) 1926

7 Kunde, M M Edema, Correlation of Elastometer Findings, Disappearance Time for Intradermally Injected Salt Solution, Urinalysis and Nitrogen Retention of Blood in Edema, *Arch Int Med* **38** 57 (July) 1926

8 Lash, A F *Surg Gynec Obst* **43** 40, 1926

9 Guggenheimer, H, and Hirsch, P *Klin Wchnschr* **5** 704, 1926

Results of Intradural Salt Solution, Seven of Whom Were Suffering from Nephritis

Blood Chemistry

| Case | Sex | Race | Age | Diagnosis | Date of Test | Disappearance in Minutes | | Palpable I dema in | | Urinary Observations | | | Total | | Uric Acid, Mgr per 100 Cc Blood | Sodium Chloride, per Cent | Cholesterol, per Cent | Carbon Dioxide Capacity |
|--|-----|------|-------------------------|---|--------------|--------------------------|-----|--------------------|-----|----------------------|-----------------|-------------------|---|--------------------------------|---------------------------------|---------------------------|-----------------------|-------------------------|
| | | | | | | Fore arm | Leg | Fore arm | Leg | Alb-min | Red Blood Cells | White Blood Cells | Nonprotein Nitrogen, Mgr per 100 Cc Blood | Ore-tine, Mgr per 100 Cc Blood | | | | |
| 1 | O | P | 11 years | Chronic nephritis | 10/9/26 | <1 | <1 | ++ | ++ | ++ | ++ | ++ | 128.0 | 7.8 | 8.0 | 0.53 | 0.21 | |
| | | | | | 10/10/26 | | | | | | | | | | | | | |
| | | | | | 10/22/26 | | | | | | | | | | | | | |
| | | | | | 10/23/26 | | | | | | | | | | | | | |
| (Died) | | | | | | | | | | | | | | | | | | |
| An obese, muscular man complaining of dyspnea of 7 years' duration, edema of the extremities and serotum of one week's duration. Examination revealed massive edema of the arms, legs, palms, serotum and abdominal wall. During stay in hospital he became progressively worse, had severe headache, became irrational and died. Autopsy observations were chronic glomerulonephritis, generalized anasarca, bilateral pulmonary edema, cerebral edema, early fibrinous pericarditis | | | | | | | | | | | | | | | | | | |
| 2 | A | M | 54 years | Chronic interstitial nephritis and hypertension | 10/16/26 | 54 | 10 | — | — | + | — | — | 10.0 | 8.0 | 2.0 | 0.60 | 0.17 | |
| | | | | | 11/8/26 | 55 | 15 | — | — | + | — | — | | | | | | |
| A poorly developed, poorly nourished man complaining of asthenia and generalized pains of 1½ months' duration. Examination revealed pallor under the eyes but no edema of the extremities. Skin dry and anemic, heart slightly enlarged without murmurs and a regular rhythm, liver 3 cm below the costal margin, Wassermann test negative, blood pressure systolic 160, diastolic 80, red blood cells, 2,100,000, white blood cells, 5,000, hemoglobin, 10 per cent, no abnormal blood cells. He did not improve under treatment | | | | | | | | | | | | | | | | | | |
| 3 | S | O | 12 years | Impending uremia, chronic nephritis with hypertension | 10/25/26 | 61 | 50 | — | — | ++ | — | — | 63.4 | 12.0 | 2.2 | 0.19 | 0.10 | |
| | | | | | 10/28/26 | 61 | 50 | — | — | ++ | — | — | 67.0 | 55.0 | 2.2 | 0.19 | 0.10 | |
| | | | | | 11/1/26 | 67 | 60 | — | — | ++ | — | — | 55.0 | 33.0 | 2.0 | 0.18 | 0.11 | |
| | | | | | 11/11/26 | 54 | 43 | — | — | + | — | — | | | | | | |
| A well nourished, rather labby man, admitted in a semicomatose, incoherent condition. Physical examination was essentially negative, blood pressure on admittance systolic 220, diastolic 150, Wassermann test negative, red blood cells, 6,900,000, white blood cells, 21,900, hemoglobin, 100 per cent. He rapidly improved. On becoming rational had a marked speech defect and impairment of vision, both of which disappeared with convalescence. Blood picae since on discharge systolic 160, diastolic 110 | | | | | | | | | | | | | | | | | | |
| 4 | J | O | female colored 28 years | Chronic nephritis with uremia, pulmonary tuberculosis, fibrous pericarditis, arteriosclerosis | 10/28/26 | 75 | 58 | — | — | +++ | — | — | 176.0 | 113.0 | 9.2 | 0.51 | | |
| | | | | | 11/1/26 | | | — | — | ++ | — | — | 193.0 | 105 | 10.0 | | | |
| | | | | | 11/9/26 | 50 | 43 | — | — | ++ | — | — | 211.0 | 176.4 | 8.0 | 15.0 | | |
| | | | | | 11/15/26 | 45 | 40 | — | — | ++ | — | — | 215.0 | 7.0 | 16.0 | | | |
| | | | | | 11/18/26 | 40 | 33 | — | — | ++ | — | — | 322.0 | 172.0 | 9.0 | 12.0 | 0.60 | 0.13 |
| A slender emaciated woman, dyspneic, complaining of cough, headache, tinnitus, hemoptysis of 9 months' duration, epistaxis, vomiting of 2 weeks' duration. Physical examination revealed an enlarged heart with a systolic murmur heard at the apex, lungs impaled, apical resonance with inspiratory crackles and moist rales in them, no edema. She was at all times mentally acute and remained about in the same condition while in the hospital. Wassermann test negative, blood pressure systolic 200, diastolic 120, red blood cells, 2,600,000, white blood cells, 11,600, hemoglobin, 40 per cent | | | | | | | | | | | | | | | | | | |
| 5 | K | L | female white 45 years | Chronic interstitial nephritis with hypertension | 11/8/26 | 45 | 30 | ++ | ++ | ++ | — | — | 57.3 | | 3.0 | | | |
| | | | | | 11/10/26 | 41 | 32 | ++ | ++ | ++ | — | — | 52.0 | | 2.3 | | | |
| | | | | | 11/12/26 | 49 | 33 | ++ | ++ | ++ | — | — | 10.0 | 20.3 | | | | |
| | | | | | 11/22/26 | 52 | 38 | ++ | ++ | ++ | — | — | | | | | | |
| A rather obese woman not acutely ill, complaining of intermittent swelling of the ankles, anorexia, headache, and pain in the right lumbar region. Physical examination was essentially negative, Wassermann test negative, blood pressure systolic 110, diastolic 110, white blood cells, 10,800. Uneventful improvement | | | | | | | | | | | | | | | | | | |

6 C A Generalized arterio- 11/17/26 93 74 — — — — — 43 0 33 0 0.2 2.1 0.45 0.23
 male sclerotic, chronic 11/20/26 77 75 — — — — — — — — — — — — —
 colored nephritis, syphilitic 11/30/26 89 83 — — — — — — — — — — — — —
 37 years aortitis, aortic insufficiency

A heavily muscled man complaining of headaches, dizzy spells, dyspnea, and frequency of urination, all of 1 month's duration. Physical examination revealed cardiac disease, blood pressure systolic 170, diastolic 100, Wassermann test positive, red blood cells, 3,530,000, white blood cells, 11,000, hemoglobin, 80 per cent. Was relieved of his symptoms during stay in hospital, blood pressure and urine remained unchanged.

7 S T Chronic parenchymatous nephritis, hydrothorax, isetes, vesicovaginal fistula 11/10/26 15 12 — — — — — 68.8 47.2 3.3 2.8
 female 11/16/26 11 12 — — — — — — — — — — — — —
 white 11/18/26 11 12 — — — — — — — — — — — — —
 68 years 11/21/26 5 5 — — — — — — — — — — — — —
 12/10/26 <1 <1 — — — — — — — — — — — — —

A rather obese, flabby woman complaining of swelling of the ankles, incontinence of urine and burning on urination. Physical examination revealed marked edema of the extremities, shifting abdominal dulness, edema about the face and of the abdominal wall, fullness over both pulmonary bases, breath sounds feeble, heart enlarged to the left, Wassermann test positive, blood pressure systolic 170, diastolic 100. Treatment with digitalis and eusims, the patient to perspire resulted in temporary improvement, then became progressively worse until death.

8 B D Chronic glomerulotubular nephritis, diphtheritic ulcers of sigmoid, hydrothorax, hydroperitoneum, cardiac hypertrophy 11/8/26 — — — — — — — 212.0 177.0 8.5 18.0
 female 11/9/26 — — — — — — — — — — — — —
 colored 11/10/26 — — — — — — — — — — — — —
 31 years 11/13/26 30 33 — — — — — — — — — — — — —
 11/15/26 20 18 — — — — — — — — — — — — —
 11/16/26 — — — — — — — — — — — — —
 (died)

A well developed, moderately emaciated woman complaining of dyspnea, orthopnea, swelling of the ankles, asthenia, nausea and vomiting of 2 months' duration. Physical examination revealed moderate edema of the extremities, in enlarged, tender liver, hydrothorax and a transversely enlarged heart. Patient had frequent attacks of vomiting, increasing dyspnea, and weakness and a rapidly diminishing mental acuity preceded death, a uremic frost was present on the day before death. The Wassermann test was negative, blood pressure systolic 180, diastolic 125, red blood cells, 2,070,000, white blood cells, 12,600, hemoglobin, 40 per cent.

9 A G Acute parenchymatous nephritis (nephrosis?) 11/18/26 4 4 — — — — — — — 5.0
 male 11/20/26 3 3 — — — — — — — — — — — — —
 white 11/23/26 1 1 {R+++} L++ 35.0
 18 years 11/30/26 {R<1} L++ — — — — — — — — — — — — —
 12/10/26 {R<1} L++ — — — — — — — — — — — — —
 12/13/26 {R<1} L 21 — — — — — — — — — — — — —
 (died)

Dyspnea of 2 months' duration, and swelling of the extremities and trunk of 1 week's duration. Physical examination revealed marked edema of arms, legs, face, trunk and genitalia, isetes, a few moist rales over the right chest. Patient's condition remained about the same until death, with the exception of the gradual disappearance of edema in the left arm. The two arms showed a marked difference in the time of disappearance of the wheal.

10 P H Acute nephritis 1/21/27 60 85* — — — — — — — 150.0 100.0 3.3 8.0 0.54 0.295 3.0
 male 1/22/27 60 70 — — — — — — — — — — — — —
 white 1/21/27 80 75 — — — — — — — — — — — — —
 11 years 1/25/27 70 65 — — — — — — — — — — — — —

An obese, muscular man, presumably well up to three weeks before admission. Complaint: shortness of breath, cough, hemoptysis, hoarseness, edema of ankles, all following a cold three weeks previously. Not much change in edema during the ten days spent in hospital. Blood pressure systolic 170, diastolic 80, Wassermann test negative. Patient died Jan 27, 1927. There was pitting edema both in the thigh and leg, but none in the knee region, which was used in the tests on the leg.

INDIVIDUAL CASES

In cases 1 and 12, the patients had an extreme degree of anasarca. The results were as expected—an extremely short disappearance time, less than one minute, in fact, it was practically impossible to raise a wheal by the injection of salt solution. Both patients were moribund.

In cases 2, 3, 4, 5 and 6, cases of nephritis without edema, the disappearance time was not much shortened either in the arm or in the leg, but was usually somewhat longer in the arm. In case 7, the amount of edema was about equal in the arm and in the leg, and the disappearance time was approximately the same.

In case 8 the patient had nephritis with a mild degree of edema, and there was considerable decrease in the disappearance time. This case resembles case 4 in many respects, in both the retention of nitrogen and the blood pressure were high, they differ in that there was an absence of edema in case 4, which caused a marked difference in the disappearance time in the two cases. In both patients the disappearance time decreased as they became clinically worse, although evident change in the degree of edema did not occur.

In case 9, on admission to the hospital, the patient had marked edema in both the upper and lower extremities, and the disappearance time was correspondingly short. Later the edema of the left forearm subsided somewhat and this was associated with an increase in the disappearance time.

In case 10 a case of acute nephritis, there was palpable edema of both legs, which was less in the thighs and absent in the region of the knee and in the arms. The disappearance time was long both in the forearm and in the knee region. Unfortunately, in this case the test was not carried out in the region of the calf when palpable edema was present. As permission for necropsy was not obtained, it is difficult to rule out cardiac edema.

In case 11 we were dealing with chronic nephritis in a comparatively young person. Although there was no palpable edema during the time that the salt solution tests were carried out, the disappearance time in both the arm and the leg was remarkably short and approximately constant. Both the present study and the results obtained by Kunde⁷ seem to show that there is no relationship between the short disappearance time and the high degree of retention of nitrogen. The relationship to the low carbon dioxide capacity of the blood is suggestive but not certain, because the analysis was carried out only one day before the patient's death.

In case 13, the patient gave a typical history leading to a clinical diagnosis of chronic nephritis with hypertension. On postmortem examination, chronic glomerulonephritis, marked concentric hypertrophy of the heart and moderate atheromatous degeneration of the aortic,

tricuspid and mitral leaflets were found. The patient spent about three weeks in the hospital, during which time there was no palpable edema. The disappearance time in both the arm and the leg was within normal limits soon after admission, but, as seen from the results in the table, there was a steady decline with a sharp break about two weeks after the patient was admitted. The patient had been placed on a treatment with sodium bicarbonate (1 drachm [3.885 Gm.] three times a day) on the day of admission to the hospital, but this was discontinued three days before the patient's death. As is seen from the results of a chemical examination of the blood made seven days after admission to the hospital, the patient was in a state of alkalosis. Nearly a week later, a sudden diminution occurred in the disappearance time. At the same time, the patient began to show marked symptoms of nervousness and continuous intense clonic twitchings of the musculature, which was especially pronounced in the extremities. In the next few days the disappearance time fell still lower, to two and three minutes in the forearm and leg, respectively. At the same time, while the degree of nitrogen retention was constantly increasing, the carbon dioxide capacity remained at the same high level. The patient, meanwhile, complained of great thirst, the twitchings continued, and he apparently developed a psychosis. Such was his condition three days before his death, when the administration of sodium bicarbonate was stopped and sodium acid phosphate was substituted. Two days later, the twitching of his muscles subsided and his mind cleared up considerably, at the same time the disappearance time rose somewhat and the carbon dioxide capacity fell to 82.6. As the patient died the day following the last test, one can only speculate whether the disappearance time would have increased much more on continued treatment with the acid salt.

In case 14, the patient came to the hospital with generalized edema, especially marked in the lower extremities. Cardiac symptoms were not observed, and the symptoms were thought to be caused by an acute exacerbation of chronic parenchymatous nephritis. The edema quickly subsided on treatment with diuretin, and with it the disappearance time of the salt solution was increased. The disappearance time both in the arm and the leg was normal in less than a week after treatment was started.

In case 15, the patient's symptoms led to a diagnosis of nephritis with hypertension. He had had scarlet fever four years previously, and had been edematous for about two weeks afterward. On admission to the hospital, there was no palpable edema, and the disappearance time was normal in the arm but was low in the leg. The disappearance time in the leg remained at about the same level during the twelve days the patient spent at the hospital, but became still shorter on the last day of the

patient's life. The disappearance time in the arm dropped to the low level of from sixteen to eighteen minutes in the last afternoon when there was a sudden rapid change for the worse and he died a few hours later. What the relation was between the low carbon dioxide capacity of the blood and the drop in the disappearance time in the forearm in the last few hours is merely to be surmised. The low disappearance time in the leg is perhaps explainable by circulatory changes.

The patient whose condition is reported in case 16 gave a typical history of nephritis and the physical observations were that he was suffering from chronic nephritis with hypertension. His heart and liver were enlarged; there were marked sclerotic changes in the vessels and a hemorrhagic exudative neuroretinitis. He had had swelling of the ankles for the nine months previous to admission, but there was no edema during the time these tests were carried out.

The disappearance time in the leg was low while the patient was in the hospital whether or not this was due to circulatory disturbances cannot be told with certainty.

The patient discussed in case 17 swallowed 60 grams (3.90 Gm.) of mercuric chloride in an attempt to commit suicide. Urinary suppression immediately followed the degree of retention of nitrogen constantly increased but the time of disappearance of the salt solution remained unchanged at from thirty to forty minutes.

In case 18 the patient gave a definite history of syphilis and intense antisyphilitic treatment. On admission, there was marked edema of the lower half of the body, but there was no palpable edema in the upper extremities. The time required for the disappearance of wheal was very short in the legs (one-half minute) and moderately short (twenty minutes) in the arms. Attempted treatment was of no avail and the edema extended to the forearm in the last days of the patient's life when the disappearance time dropped accordingly. As indicated by the results given in the table the degree of retention of nitrogen at the end of the patient's life was not much greater than on admission.

COMMENT

The cases of nephritis presented here are insufficient in number to permit the drawing of sweeping conclusions although they present a few interesting points.

As stated before the fundamental fact of the rapid disappearance of the elevation made by the intradermal injection of physiologic sodium chloride solution in nephritic edemas, is again confirmed by these studies. The disappearance time in any particular case usually varies during the course of the disease with the changes in the degree of the edema. A persistently low disappearance time usually indicates a bad prognosis.

There is no close relationship apparent between the degree of the edema and the disappearance time, on the one hand, and the retention of nitrogen and the content of sodium chloride and cholesterol in the blood, on the other.

The disappearance time may also be short in cases of nephritis without palpable edema, here, too, no relationship is seen between this short disappearance time and the observations made on the blood during chemical examination. There may, however, be a relationship between the carbon dioxide capacity of the blood and tissues and the disappearance time of the wheal—either a prolonged acidosis or alkalosis leading to a diminished disappearance time.

The influence of the carbon dioxide capacity deserves further study. The examples of a short disappearance time of the wheal in cases of nephritis, in which either acidosis or alkalosis developed in the course of treatment, are rather suggestive, but not conclusive.

In nephritis associated with arteriosclerosis, the circulatory factor must be taken into consideration, especially in interpreting the low results frequently obtained in the region of the leg. In this connection, the work of Cohen and his co-workers, to which reference has been made, is suggestive.

In the case of mercuric chloride poisoning reported in this article, there seemed to be no relationship between the time of the disappearance of the wheal, the urinary output, which was low at all times, and the retention of nitrogen, which was constantly progressing.

SUMMARY

A study of the intradermal salt solution test was made in eighteen cases of nephritis in adults with the following results:

- 1 The wheals caused by the salt solution disappeared in less than thirty minutes, except in one case (case 13, alkalosis), only when edema or a history of edema was present.

- 2 A decreasing disappearance time was associated with an unfavorable course of the condition, an increasing disappearance time with improvement, a very short disappearance time, which persisted in spite of treatment, was of bad prognostic significance.

- 3 There was no close relationship between the retention of nitrogen and the sodium chloride and cholesterol content of the blood, on the one hand, and the disappearance time on the other.

- 4 In cases in which the carbon dioxide capacity was determined, and evidence of either severe acidosis or alkalosis was found, there was also a marked shortening of the disappearance time, even in the absence of palpable edema. More examples of these types should be examined.

INTESTINAL ABSORPTION

A SEARCH FOR A LOW RESIDUE DIET^{*}

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There are many occasions when physicians or surgeons wish to use a diet with the least possible residue, particularly in the treatment of patients with diarrhea and following operations about the rectum or anus. If the fecal residues can be made small enough, and if defecation can be postponed for a week or more, not only will the patient be spared much distress, but healing wounds can be kept clean. Considering the importance of this problem, it is surprising to find practically no mention of it in most of the well known textbooks on dietetics.

According to Prausnitz,¹ Bischoff and Voit,² Muller,³ and Rubner,⁴ so long as the foods given are completely utilized, the amount of feces voided will remain about the same with different diets. As is well known, a considerable portion of the fecal material is made up of dead bacteria and intestinal secretions, so, even during starvation, a certain amount of feces will always be formed. As one would expect, the bulk of the stools depends largely on the amount of cellulose contained in the food.

Cannon⁵ gave cats various foods mixed with bismuth and watched the progress of the material through the bowel. He concluded that proteins pass through the small intestine slowly, fats a little faster and carbohydrates fastest of all. Doubtless these differences were due partly to the varying rates with which these foods pass through the pylorus, but Cannon felt that they were due also to differences in

^{*} From the Division of Medicine, Mayo Clinic and the Division of Experimental Surgery and Pathology, The Mayo Foundation.

1 Prausnitz, Wilhelm. Ueber die Ausnützung der Kuhmilch im menschlichen Darmkanal. *Ztschr f Biol* **25**:533, 1889, Die Ausnützung der Bohner im Darmkanale des Menschen. *ibid* **26**:227, 1890, Die chemische Zusammensetzung des Kothes bei verschiedenartiger Ernährung, *ibid* **35**:335, 1897.

2 Bischoff, E., and Voit, quoted by Rubner. *Ztschr f Biol* **15**:115, 1879.

3 Müller, Friedrich. Ueber den normalen Koth des Fleischfressers, *Ztschr f Biol* **20**:327, 1884.

4 Rubner, Max. Ueber die Ausnützung einiger Nahrungsmittel im Darmkanale des Menschen, *Ztschr f Biol* **15**:115, 1879.

5 Cannon, W B. *The Mechanical Factors of Digestion*, London, Edward Arnold 1911. 227 pp.

the muscular response of the bowel. The rate of passage through the small intestine is important because it may be a factor in determining the amount of digestion and absorption with any one meal.

One of the best articles on the subject of absorption in the small intestine is by Heile,⁶ who gave a number of foods to dogs with a cecal fistula. He also studied a few patients with fistulas in the terminal ileum. With dogs on a mixed diet, undigested material began to appear at the fistula at the end of an hour, the greatest amount came through in the third and fourth hours, and by the fifth hour the bowel was clean. With lean meat, the observations were the same. With carbohydrates and fats, the extrusion began sooner, it increased rapidly and ceased after three or four hours.

Heile noticed that milk gave rise to large amounts of residue, when 126 Gm of well chopped meat was given to a dog, only 20 Gm of material came away, but when a liter of milk was given containing 130 Gm of solid material, the residue appearing at the fistula amounted to 250 Gm. Heile was impressed with the desirability of giving proteins when the colon is to be spared work. He found that when from 250 to 500 Gm of horse flesh was given to a dog, all but 2 per cent was absorbed. When he gave 75 Gm of sucrose to a dog weighing 11 Kg, it was all absorbed, but when he gave more than 100 Gm, small amounts of reducing material began to come away. One hundred grams of rice was completely absorbed.

In extensive studies of the stools of dogs, Muller showed that when the animals are not given anything but meat or meat and a little sugar, the stools differ little from those obtained during periods of fasting.

According to Babkin,⁷ Berlitzki, working with dogs with a cecal fistula, confirmed the observation of others that the giving of milk results in the prompt passage of large amounts of residue. He found that this occurred also when milk was added to foods which otherwise would have been well digested. Another substance that behaved peculiarly was raw egg albumin. The list taken from Babkin's book gives an idea of the results obtained by Berlitzki (table 1).

Babkin and Strashesko thought that it was the lactose in the milk that increased intestinal peristalsis and caused the retention of fluid within the lumen of the bowel. Harley and Goodbody, quoted by Cammidge,⁸ also comment on the tendency of milk to increase the bulk of fecal residues.

6 Heile, B. Experimentelle Beobachtungen über die Resorption im Dünn- und Dickdarm, *Mitt a d Grenzgeb d Med u Chir* **14** 474, 1905.

7 Babkin, B. P. Die aussere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1914, p. 386.

8 Cammidge, P. J. The Feces of Children and Adults, Bristol, John Wright & Sons, 1914, p. 317.

Rubner, in his classic article, gives the list of foods which he fed to young healthy men (table 2). It will be seen that the foods that were best used were meat, eggs, rice, white bread, noodles and macaroni. Less well digested were milk, cheese, fats and potatoes. The highest

TABLE 1—*Results Obtained by Beilitzki with Various Kinds of Food (From Babkin)*

| Kind of Food | Amount Collected After Ten Hours, Cc | Per Cent Excreted |
|---------------------------|--|----------------------|
| 600 cc water | 97 | 16 |
| 400 Gm meat | 208 | 50 |
| 200 Gm bread | 343 | 171 |
| 600 cc oatmeal (water) | 80 | 13 |
| 600 cc oatmeal plus milk | 253.5 | 42.2 |
| 600 cc rice plus milk | 324.5 | 54.0 |
| 600 cc mush plus milk | 244.0 | 40.6 |
| 600 cc milk | 171.1 | 28.5 |
| 600 cc. skimmed milk | 224.7 | 37.5 |
| 600 Gm curds | 25.6 | 4.3 |
| 100 Gm butter | 4.7 | 4.7 |
| 100 cc olive oil | 4.0 | 4.0 |
| 300 Gm raw egg albumin | 79.5 | 26.5 |
| 300 Gm boiled egg albumin | 23.5 | 7.8 |
| 300 Gm raw egg-yolk | 17.5 | 5.8 |

TABLE 2—*List of Food Given by Rubner to Young Healthy Men (From Rubner)*

| Food | Percentage Lost in the Stools | | |
|------------------|-------------------------------|----------|------|
| | Dry Substance | Nitrogen | Ash |
| White bread | 3.7 | 18.7 | 17.3 |
| White bread | 5.2 | 25.7 | 25.4 |
| Rice | 4.1 | 20.4 | 15.0 |
| Macaroni | 4.3 | 17.1 | 24.1 |
| Macaroni | 5.7 | 11.2 | 22.2 |
| Meat | 4.7 | 2.5 | 15.0 |
| Meat | 5.6 | 2.8 | 21.2 |
| Noodles | 4.9 | 20.5 | 20.9 |
| Egg plus meat | 5.1 | 2.6 | 18.1 |
| Egg, hard boiled | 5.2 | 2.9 | 18.4 |
| Milk plus cheese | 6.0 | 3.7 | 26.1 |
| Milk plus cheese | 6.8 | 2.9 | 30.7 |
| Milk plus cheese | 11.3 | 4.9 | 55.7 |
| Corn | 6.7 | 15.5 | 30.0 |
| Butter, 240 Gm | 6.7 | 11.3 | 20.0 |
| Milk | 7.8 | 6.5 | 48.8 |
| Milk | 8.4 | 7.0 | 46.8 |
| Milk no 5 | 8.4 | 7.0 | 46.8 |
| Milk no 7 | 9.4 | 12.0 | 44.5 |
| Milk no 6 | 10.2 | 7.7 | 48.2 |
| Lard, 100 Gm | 8.5 | 12.1 | 28.5 |
| Lard, 200 Gm | 9.2 | 14.0 | 25.1 |
| Potatoes | 9.4 | 32.2 | 15.8 |
| Cabbage | 14.9 | 18.5 | 19.3 |
| Black bread | 15.0 | 32.0 | 36.0 |
| Carrots | 20.7 | 39.0 | 33.8 |

percentage of loss was found with certain samples of milk and cheese, with cabbage, black bread and carrots.

If a low residue diet is desired, Cammidge advises the use of small amounts of white bread and butter, white of egg, lean meat and well cooked rice. Carter, Howe and Mason⁹ mention the fact that when

⁹ Carter, H. S., Howe, P. E., and Mason, H. H. Nutrition and Clinical Dietetics, Philadelphia, Lea & Febiger, 1921, p. 47.

milk is added to the diet it will cause considerable increase in the fecal output. They think this is due to unabsorbed calcium, phosphorus and perhaps nitrogen.

At St. Mary's Hospital, Rochester, Minn., the low residue diet prescribed by the dietitian, Miss Smith, is made up of strained fruit juices, broth, tea, coffee, sugar, candy made of sugar alone and jello made with strained fruit juices. Such a diet works satisfactorily, and patients easily go for eight days without a bowel movement.

REPORT OF EXPERIMENTS

The animals used in these studies were prepared by the following method. As is well known, it is not easy to make an ileal fistula in a dog and have him live in comfort. The surrounding skin tends to become excoriated, the operative wound becomes infected, and healing is retarded or made impossible. To avoid this difficulty, animals were operated on as follows. Under ether anesthesia, the last 25 cm. of ileum was resected together with the colon up to a point 6 cm. from the anus. End to end anastomosis was then performed on the ileum and rectum. In one of the three animals on which our observations were made 10 cm. of the colon had to be left on account of the situation of some large arteries. Animals were thus obtained which to all intents and purposes had a fistula of the terminal ileum, but which were much easier to take care of because they possessed a normal anus and a continent sphincter. It also greatly simplified the problem of collecting specimens of feces.

During this series of experiments, three animals were used: dog 1, a fox terrier weighing 5.8 Kg. at the beginning of the experiment; dog 2, a mongrel, weighing 9.9 Kg.; and dog 3, a mongrel, weighing 15.6 Kg. Largely perhaps on account of the daily experimenting with single foods, the animals tended to lose weight, but this tendency was counteracted by giving them plenty of food on Sundays and during occasional rest periods.

The animals were fed only once a day, about 8:30 a. m. One dog ate greedily anything that was given him, but the other two sometimes objected to certain foods and had to be fed either by tube or by dropping the material on the back of the tongue. Within from fifteen to thirty minutes after feeding, the animals were fastened comfortably either in the lateral recumbent or in the crouching position. Samples were collected at hourly intervals for eight hours, and the animals were then put into metabolism cages. In the morning any fecal material found on the floor of the cage or in the rectum, was examined microscopically; if it contained food remnants, it was added to the samples from the day before, but if it was a typical, dark, foul-smelling, amorphous "hunger stool," it was thrown away. Ordinarily, with foods that did not contain cellulose, there was little if any residue after the first eight hours.

The fecal material was collected with the help of a glass tube, 15 cm. in length and about 1 cm. in diameter to which petrolatum had been applied; this tube was passed through the anus. Any fluid present immediately flowed out, and solid feces were then forced into the tube by the straining of the animal. During the first few weeks, some stools were voided normally, but later the animals practically always waited until the tube was passed. Any fecal material adhering to the side of the tube was washed out with a measured amount of distilled water, and the whole specimen was then weighed. Note was made of the color, odor, consistency, reaction and microscopic appearance of the material, and the specimen was then dried to constant weight.

FASTING RESIDUES

When food was not given for twenty-four hours, only a small amount of dark brown material appeared. It had the consistency of thin mush and the odor was offensive like that of the usual dog's stool. Table 3 shows the amounts of moist and dry material excreted in twenty-four hours by each of the three dogs (chart 1). The reaction was always neutral to litmus paper. Microscopic examination showed granular material with occasional epithelial cells.

TABLE 3—Amounts of Moist and Dry Material Excreted During Twenty-Four Hours

| Dog | Weight, Kg | Total Fecal Output in Grams in 24 Hours | | Output of Moist Stool for Each Kilogram of Body Weight |
|-----|---------------|--|------|---|
| | | Moist | Dry | |
| 1 | 6.8 | 9.16 | 2.17 | 1.35 |
| 2 | 9.9 | 15.37 | 2.47 | 1.16 |
| 3 | 15.6 | 18.09 | 3.09 | 1.55 |

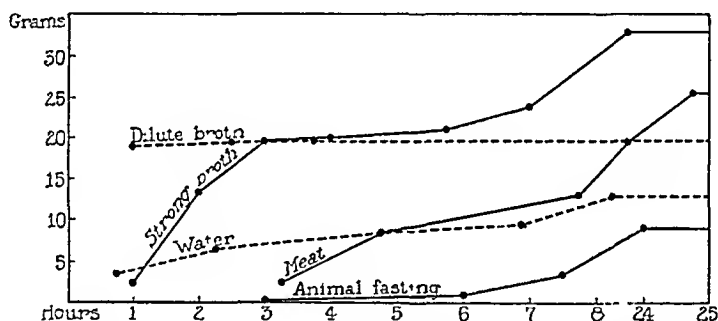


Chart 1—The rate and quantity of excretion of moist residues (expressed in grams) for meat and broth, also the amount of fecal material obtained during fasting and after the giving of water.

CHARACTERISTICS OF FECAL MATERIAL WITH DIFFERENT DIETS

When the animals were fed with protein foods, meat, liver, gelatin and concentrated broth, the stools resembled closely those obtained from fasting animals. Only once was the reaction faintly alkaline, and that was when hashed meat was used. When the animals were fed on gelatin, the stools were light colored and had little odor, when meat was used, they were dark and usually fetid.

Food consisting mainly of carbohydrate, such as rice, bread, banana, apple and sugar gave rise to light canary, golden yellow or russet colored stools. They were mushy in consistency but somewhat thicker than the protein stools. They gave off little odor. Those obtained after feeding raw banana were fluid. After meals of dextrose, sucrose and lactose, the stools contained reducing substances.

When the animals were given lard, the stools were generally yellow, mushy and putrid, when they were given butter, the stools were watery and soapy. In one dog, who vomited some of the butter, neutral fat could be seen in the stool. The fatty stools did not seem to contain more bile than others.

RATE OF PASSAGE

Protein—From 140 to 300 Gm of lean meat or liver were fed, representing from 13 to 22 Gm for each kilogram of body weight. Although the rate of passage varied even in the same animal on different days, it was usually slow, in some experiments, nothing appeared at the anus for four and a half hours. Gelatin and hard boiled egg went through the bowel slowly, like meat, but raw egg albumin went through rapidly (chart 2).

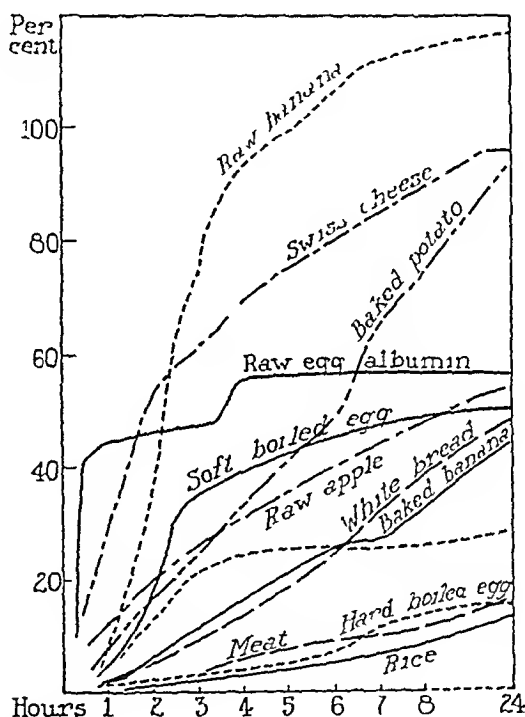


Chart 2—Percentages of the amounts eaten, the rate and amount of excretion, of moist fecal residues from various foods. Most of the curves represent averages from several experiments.

Carbohydrate—From 150 to 350 Gm of boiled rice, farina, bread or baked potato were given at one time. This represented from 9.6 to 33.6 Gm for each kilogram of body weight. The residues from rice appeared early, but, on the whole, they came through even more slowly than did those from meat. The residues from the other carbohydrate foods usually came through rapidly.

Fats—Pure lard and butter were given in amounts of from 68 to 156 Gm or about 10 Gm for each kilogram of body weight. In

only one dog did this amount of butter cause nausea, and in this animal the material went through so rapidly that some of it was untouched by the digestive juices. Butter passed through the small intestine about as fast as some carbohydrates, but lard passed through at a rate intermediate between that of protein and carbohydrate. These experiments with protein, carbohydrate and fat give considerable support to Cannon's observations.

Fruits—Canned pineapple, raw and baked apple with the skin removed, raw and baked banana, and purée of prunes were given in amounts of from 13 to 22 Gm. for each kilogram of body weight. The banana and pineapple were cut into small pieces, and the apple was passed through a meat chopper. The residues from the bananas, apples and prunes came through rapidly, in from one half to three fourths of an hour. The residue from the pineapple began to appear two and a half hours after the feeding, and it kept on appearing for twenty-eight hours or more. The food was little affected by the digestive juices.

Liquid Foods and Water—Water given by stomach tube in amounts representing 36.7 cc. for each kilogram of body weight seemed to wash through a little more material into the terminal ileum, or perhaps it increased the amount of excretion into the bowel (chart 1). The amounts of feces obtained for each kilogram of body weight in the three dogs given water were 1.91, 1.37 and 2.38 Gm. Without water the figures were 1.35, 1.16 and 1.55 Gm. Strained broth, so concentrated that it would jelly, was given in amounts of 36.7 cc. for each kilogram. As may be seen from chart 1, it seemed to be stimulating to peristalsis, so that the residues came through more rapidly and in larger amounts than did those of its constituents, water and meat. Ordinary thin broth ran through the bowel even more rapidly, so Heile's experience with soups is confirmed.

Sugars—When we gave 250 cc. (36.7 cc. for each kilogram) of a 4.2 per cent solution of lactose, corresponding to the concentration found in milk, the first residues appeared within fifteen minutes, and the rate of progress through the bowel was so rapid that nothing could be obtained after four and a fourth hours. This result so closely duplicated those of Strashesko that no further experimenting was done with lactose. The giving of 343 cc. of a 33 per cent solution of dextrose caused material to appear at the anus within thirty minutes. Progress was not so rapid as with lactose, but the bowel was empty after four and a half hours. In another experiment, 343 cc. of a 33 per cent watery solution of "karo" was given; material appeared in thirty minutes, but progress was slower than with pure dextrose, and most of the residue was obtained between the fourth and sixth

hours After that the excretion stopped Excretion was rapid also if the animal was given 109 cc of a 50 per cent solution of sucrose, but residues kept coming away for seven hours

Milk—Whole milk was given in amounts of 367 cc for each kilogram The first specimen appeared in thirty minutes, and at the end of three hours most of the residues had passed No constant difference could be observed in the behavior of raw and boiled milk, which is of interest in view of the widespread belief that boiled milk

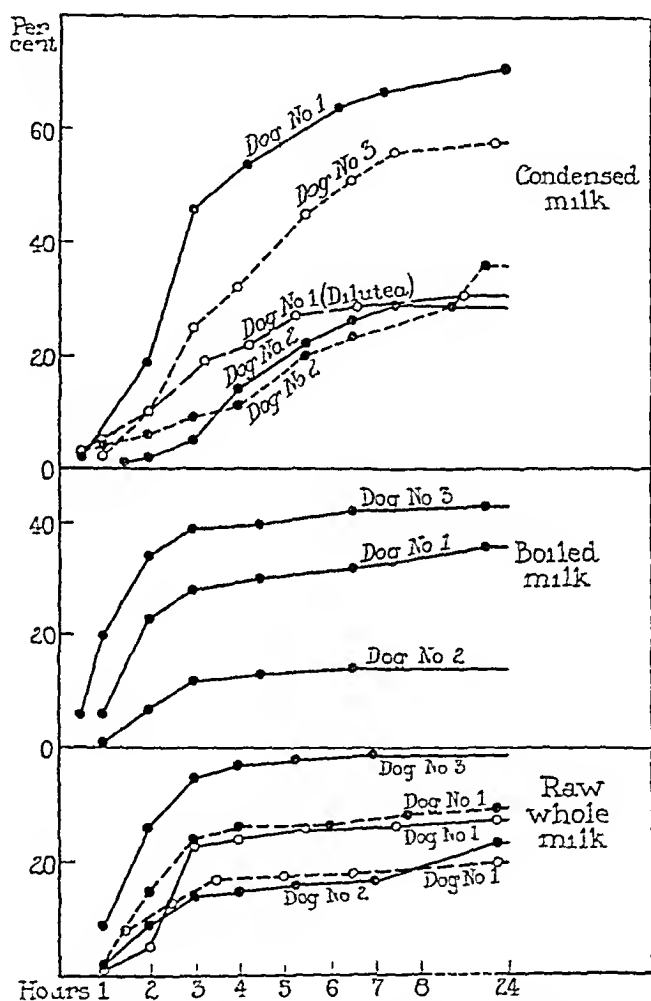


Chart 3—Percentages of the amounts eaten and the rate and amount of excretion of moist residues from fresh, boiled and condensed milk

is particularly efficacious in the treatment of diarrhea An interesting peculiarity about the excretion of milk residues, well illustrated in chart 3, is the marked divergence in the results obtained with the three dogs, the shape of the curves is the same in each instance, but dog 2 always digested the milk better than did dogs 1 and 3 This marked difference in the resorptive powers of the animals was more constant and striking with milk than with any other food As will be seen from chart 4, it was much less apparent when milk was added to

other foods, such as farina, but even then the digestive powers of the dogs fell into the same sequence Heile noticed that some of his dogs did not digest food as well at some times as they did at others, and he thought the difference was due to the presence of enteritis, but this can hardly be the explanation for the differences obtained in our experiments Condensed milk (Carnation brand) was given, either undiluted or diluted with equal parts of water, in amounts of from 21.7 to 44 cc for each kilogram of body weight The residues came through more slowly at first, so that the curves of excretion are different from those

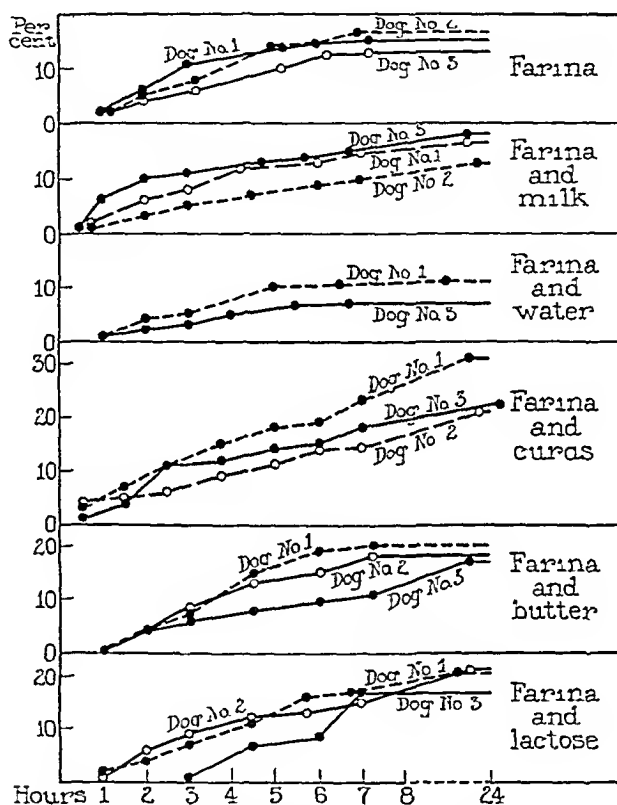


Chart 4—Percentages of the amounts eaten, and the rate and amount of excretion of moist residues from farina, from farina and milk and from some of the constituents of milk

obtained with fresh milk The condensed milk was not digested as well as was the fresh milk

Swiss cheese was given grated in amounts of 26.4 Gm for each kilogram The rate of progress was rapid, and within thirty minutes enormous amounts of fluid residue were obtained (chart 2) Even after five and a half hours, the fecal output was still large Cottage cheese (grade A, apparently full of fat) was given in amounts of from 22 to 29.4 Gm for each kilogram The time of appearance of the residues was variable, in one experiment being as late as the fifth hour, and the curve of excretion was flat like that of meat

INFLUENCE OF MILK AND MILK CONSTITUENTS ON THE DIGESTION OF OTHER FOODS

In view of the decided statements made by Berlatzki and others with regard to milk, it seemed advisable to check their results with care. A number of experiments were carried out first to establish the normal rate of passage for cooked farina. With 22 Gm for each kilogram of body weight the residues appeared early, as one would expect with a carbohydrate food. When an equal amount of whole milk was added, there was little change in the rate of progress, in one experiment it was considerably accelerated, but in another it was a little slower than usual. Chart 4 shows the results with the three dogs. In order to determine whether more pronounced effects could be obtained with any constituent of the milk, the dogs were given, besides farina, amounts of water, butter, curd and lactose equal to those contained in the milk given in the previous experiments. It was found that water somewhat increased the rate of progress of food, while butter and lactose had no constant effect, lactose increased the total amount excreted. When crude casein (made by adding junket to milk, expressing the whey through cloth for twenty-four hours, and washing for a short time in water) was added to the farina, the rate of progress was slightly accelerated, and the total amount of moist residue was considerably increased. The addition of milk to bread regularly decreased the percentage of moist residue as did the addition of broth to bread.

From this work it appears that, at least in the dog, the addition of milk to other foods does not interfere with digestion as much as Berlatzki thought, what interference there is seems to be due to casein or lactose. More work is needed to show why casein in the form of cottage cheese was well digested, while in the form of junket or Swiss cheese it was poorly digested.

THE AMOUNT OF RESIDUE WITH DIFFERENT FOODS

Table 4 shows the percentage of moist and dry residues obtained after the giving of various foods. These foods have been arranged so far as possible in the order of their digestibility, as judged by the percentage of moist residue appearing at the anus. Among those with the least residue are gelatin, sucrose, dextrose, "kalo," concentrated broth, hard boiled egg, meat, liver, rice, farina and cottage cheese, among those with the largest residues are fruits, potatoes, bread, lard, butter, Swiss cheese, soft boiled egg, raw egg albumin, milk and lactose.

The lowest dry residues were seen with dextrose, sucrose, gelatin, liver, meat, bread and milk, lard and butter. The largest dry residue was 85.9 per cent, seen with raw egg albumin. Other high dry residues, approximately 57 per cent, were seen with potato, raw banana, lactose, raw apple and broth.

TABLE 4—Percentage of Moist and Dry Residues Obtained with Various Foods

| Dog | Food | Forced Feeding | Total Amount of Food, Gm | | Per Kilo-gram | Total Residue, Gm | | Percentage of Residue | | Percentage of Water |
|-----|------------------------|----------------|--------------------------|-------|---------------|-------------------|-------|-----------------------|------|---------------------|
| | | | Moist | Dry | | Moist | Dry | Moist | Dry | |
| 2 | Gelatin | Yes | 364 3 | 71 2 | 36 7 | 17 22 | 2 39 | 4 7 | 3 4 | 86 1 |
| 1 | Dilute broth | No | 246 8 | 2 9 | 36 7 | 19 70 | 1 19 | 7 9 | 41 0 | 93 9 |
| 2 | Dilute broth | No | 360 0 | 4 2 | 36 7 | 35 88 | 1 79 | 9 9 | 42 3 | 95 0 |
| 3 | Dilute broth | Yes | 567 1 | 6 7 | 36 7 | 59 57 | 2 02 | 10 5 | 30 3 | 96 6 |
| 3 | Dextrose, 33 per cent | Yes | 507 7 | 171 6 | 22 0 | 53 53 | 2 83 | 10 5 | 1 7 | 94 7 |
| 3 | "Karo," 33 per cent | Yes | 507 7 | 134 2 | 24 9 | 55 70 | 7 14 | 10 6 | 5 3 | 87 2 |
| 2 | Sucrose, 50 per cent | No | 215 5 | 108 9 | 11 0 | 23 79 | 3 52 | 11 0 | 3 2 | 85 2 |
| 3 | Farina, water | Yes | 678 9 | 56 8 | 43 5 | 44 83 | 5 82 | 6 6 | 10 2 | 87 0 |
| 1 | Farina, water | Yes | 296 9 | 24 9 | 43 7 | 32 76 | 4 46 | 11 0 | 17 9 | 86 4 |
| 3 | Strong broth | No | 569 2 | 28 4 | 36 7 | 56 93 | 7 64 | 10 0 | 26 9 | 86 6 |
| 1 | Strong broth | No | 249 6 | 12 5 | 36 7 | 32 80 | 5 29 | 13 1 | 42 5 | 83 9 |
| 2 | Strong broth | No | 369 5 | 18 4 | 36 7 | 51 45 | 6 66 | 13 9 | 36 1 | 87 1 |
| 1 | Rice | Yes | 229 6 | 48 9 | 33 8 | 26 62 | 4 92 | 11 6 | 10 1 | 81 5 |
| 1 | Rice | Yes | 219 6 | 45 3 | 32 3 | 29 85 | 4 68 | 13 6 | 10 3 | 84 3 |
| 1 | Rice | Yes | 174 8 | 40 2 | 25 6 | 23 75 | 4 60 | 13 6 | 11 5 | 80 6 |
| 2 | Liver, hashed | No | 200 0 | 75 0 | 20 2 | 20 54 | 3 83 | 10 3 | 5 1 | 81 3 |
| 3 | Liver, hashed | No | 200 0 | 75 0 | 12 8 | 31 94 | 4 23 | 16 0 | 5 6 | 86 7 |
| 1 | Liver, hashed | No | 150 0 | 56 3 | 22 0 | 26 02 | 4 10 | 17 3 | 7 3 | 84 2 |
| 2 | Liver, lumps | No | 200 0 | 75 0 | 20 2 | 25 31 | 4 77 | 12 7 | 6 4 | 81 1 |
| 3 | Liver, lumps | No | 200 0 | 75 0 | 12 8 | 25 65 | 3 89 | 12 8 | 5 2 | 84 8 |
| 1 | Liver, lumps | No | 150 0 | 56 3 | 22 0 | 23 39 | 4 67 | 15 6 | 8 3 | 80 1 |
| 1 | Meat, lumps | No | 150 0 | 42 9 | 22 0 | 17 69 | 3 38 | 11 8 | 7 9 | 80 9 |
| 1 | Meat, lumps | No | 300 0 | 85 8 | 44 0 | 41 32 | 6 74 | 13 8 | 7 9 | 83 7 |
| 1 | Meat, hashed | No | 140 0 | 40 0 | 20 6 | 21 30 | 3 87 | 15 2 | 9 6 | 81 8 |
| 1 | Meat, hashed | No | 150 0 | 42 9 | 22 0 | 21 93 | 5 39 | 16 6 | 12 5 | 78 4 |
| 1 | Meat, hashed | No | 150 0 | 42 9 | 22 0 | 25 52 | 4 62 | 17 0 | 10 8 | 81 9 |
| 1 | Cottage cheese | No | 150 0 | 37 4 | 22 0 | 21 75 | 3 50 | 14 5 | 9 4 | 83 9 |
| 1 | Cottage cheese | No | 200 0 | 49 8 | 29 4 | 31 29 | 5 10 | 15 6 | 10 2 | 83 7 |
| 1 | Egg, hard boiled | No | 246 5 | 64 8 | 36 2 | 37 21 | 6 33 | 15 1 | 9 8 | 82 9 |
| 1 | Farina, broth | No | 179 8 | 25 9 | 26 4 | 21 34 | 2 43 | 11 8 | 9 4 | 88 6 |
| 1 | Farina, broth | No | 179 8 | 25 9 | 26 4 | 27 19 | 3 23 | 15 1 | 12 4 | 88 1 |
| 3 | Farina | Yes | 343 0 | 56 8 | 22 0 | 42 96 | 5 02 | 12 5 | 8 8 | 88 3 |
| 1 | Farina | Yes | 150 0 | 24 9 | 22 0 | 22 45 | 2 72 | 15 0 | 10 9 | 87 9 |
| 2 | Farina | No | 218 0 | 36 1 | 22 0 | 37 96 | 4 83 | 17 4 | 13 3 | 87 2 |
| 2 | Farina, butter | No | 225 1 | 42 7 | 22 7 | 40 08 | 4 75 | 17 8 | 11 1 | 88 1 |
| 3 | Farina, butter | No | 354 5 | 67 1 | 22 7 | 60 34 | 8 96 | 17 0 | 13 3 | 85 2 |
| 1 | Farina, butter | No | 155 0 | 29 4 | 22 8 | 30 94 | 3 39 | 19 9 | 11 5 | 89 0 |
| 2 | Farina, milk | No | 441 0 | 63 4 | 44 5 | 58 35 | 9 28 | 13 2 | 14 6 | 84 1 |
| 1 | Farina, milk | No | 303 4 | 43 6 | 44 6 | 50 71 | 6 86 | 16 7 | 15 7 | 86 5 |
| 3 | Farina, milk | No | 693 9 | 99 7 | 44 5 | 128 04 | 16 83 | 18 4 | 16 9 | 86 8 |
| 3 | Farina, lactose | Yes | 357 5 | 72 4 | 23 0 | 59 01 | 7 87 | 16 5 | 11 0 | 86 6 |
| 1 | Farina, lactose | Yes | 156 4 | 31 2 | 23 0 | 32 37 | 5 68 | 20 7 | 18 2 | 82 5 |
| 2 | Farina, lactose | No | 227 2 | 45 4 | 23 0 | 48 70 | 7 42 | 21 4 | 16 4 | 84 8 |
| 2 | Farina, casein | No | 266 7 | 54 8 | 26 9 | 55 59 | 8 33 | 20 8 | 15 2 | 85 0 |
| 3 | Farina, casein | Yes | 425 5 | 88 4 | 27 3 | 92 08 | 11 45 | 21 6 | 13 0 | 87 6 |
| 1 | Farina, casein | No | 189 2 | 39 9 | 27 8 | 58 16 | 6 83 | 30 7 | 17 1 | 88 3 |
| 1 | Milk | No | 255 7 | 31 3 | 36 7 | 50 46 | 4 83 | 19 7 | 15 4 | 90 4 |
| 2 | Milk | No | 373 3 | 45 6 | 36 7 | 85 45 | 9 95 | 22 9 | 21 8 | 88 3 |
| 1 | Milk | No | 255 7 | 31 3 | 36 7 | 68 66 | 8 23 | 26 8 | 26 3 | 88 0 |
| 1 | Milk | No | 255 7 | 31 3 | 36 7 | 75 21 | 7 67 | 29 4 | 24 5 | 89 8 |
| 3 | Milk | No | 588 1 | 71 9 | 36 7 | 227 50 | 21 54 | 33 7 | 29 9 | 90 1 |
| 1 | Lactose, 4 2 per cent | Yes | 235 4 | 10 6 | 36 7 | 66 79 | 6 02 | 22 2 | 56 8 | 91 0 |
| 3 | Bread, milk | No | 303 4 | 135 3 | 19 4 | 59 34 | 8 38 | 19 5 | 6 2 | 85 9 |
| 2 | Bread, milk | No | 303 4 | 135 3 | 30 6 | 60 91 | 10 68 | 20 1 | 7 9 | 82 5 |
| 2 | Bread, milk | No | 303 4 | 135 3 | 30 6 | 65 43 | 11 49 | 21 8 | 8 5 | 82 4 |
| 2 | Bread, milk | Yes | 303 4 | 135 3 | 30 6 | 68 50 | 12 44 | 22 2 | 9 2 | 81 8 |
| 3 | Bread, milk | No | 303 4 | 135 3 | 19 4 | 91 77 | 13 59 | 30 0 | 14 8 | 83 4 |
| 1 | Bread, milk | Yes | 303 4 | 135 3 | 44 6 | 92 54 | 13 59 | 30 5 | 10 0 | 85 3 |
| 2 | Bread, broth | Yes | 298 8 | 121 9 | 30 2 | 60 79 | 10 95 | 20 4 | 8 9 | 81 9 |
| 1 | Bread, broth | Yes | 298 8 | 121 9 | 43 9 | 76 21 | 11 60 | 25 5 | 9 5 | 84 8 |
| 3 | Bread, broth | No | 298 8 | 121 9 | 19 2 | 79 75 | 11 81 | 26 8 | 9 6 | 85 2 |
| 1 | Condensed milk diluted | No | 303 7 | 39 5 | 44 0 | 94 80 | 11 18 | 31 2 | 28 3 | 88 0 |
| 2 | Milk, boiled | No | 352 9 | 47 5 | 36 7 | 50 44 | 6 76 | 14 3 | 14 1 | 86 6 |
| 1 | Milk, boiled | No | 252 1 | 33 9 | 36 7 | 89 64 | 10 65 | 35 6 | 31 4 | 88 1 |
| 3 | Milk, boiled | No | 514 2 | 69 2 | 36 7 | 221 52 | 21 19 | 43 1 | 30 6 | 90 4 |
| 3 | Bread | Yes | 150 0 | 116 5 | 9 6 | 66 96 | 12 16 | 44 6 | 10 4 | 81 8 |
| 1 | Bread | Yes | 150 0 | 116 5 | 22 0 | 70 82 | 10 89 | 47 2 | 9 3 | 84 6 |
| 2 | Bread | No | 150 0 | 116 5 | 15 2 | 79 08 | 13 29 | 52 7 | 11 4 | 83 2 |
| 2 | Condensed milk | No | 224 8 | 56 5 | 21 7 | 64 87 | 9 28 | 28 8 | 16 4 | 85 7 |
| 2 | Condensed milk | No | 224 8 | 56 5 | 21 7 | 80 22 | 10 98 | 35 7 | 19 4 | 86 3 |
| 3 | Condensed milk | No | 355 5 | 89 4 | 21 7 | 204 93 | 23 84 | 57 6 | 26 6 | 88 3 |
| 1 | Condensed milk | No | 156 7 | 39 5 | 22 0 | 111 37 | 12 65 | 70 9 | 32 1 | 88 6 |
| 1 | Pineapple canned | Yes | 150 0 | 37 3 | 22 0 | 69 88 | 9 11 | 46 6 | 24 4 | 86 9 |
| 1 | Egg, soft boiled | No | 121 0 | 30 1 | 17 8 | 61 00 | 6 08 | 50 4 | 20 2 | 90 3 |
| 2 | Lard | No | 99 0 | 99 0 | 10 0 | 43 21 | 7 25 | 43 6 | 7 3 | 83 2 |
| 3 | Lard | No | 136 0 | 156 0 | 10 0 | 72 02 | 11 91 | 46 2 | 7 6 | 83 5 |
| 1 | Lard | No | 68 0 | 68 0 | 10 0 | 39 33 | 6 32 | 57 8 | 9 3 | 83 9 |
| 1 | Raw egg albumin | Yes | 178 5 | 21 3 | 26 2 | 100 92 | 18 34 | 56 5 | 85 9 | 81 8 |
| 3 | Banana, baked | Yes | 340 0 | 86 8 | 22 0 | 106 51 | 12 64 | 31 3 | 14 6 | 88 1 |

TABLE 4—Percentage of Moist and Dry Residues Obtained with Various Foods—(Continued)

| Dog | Food | Feed- ing | Total Amount of Food, Gm | | Per Kilo- gram | Total Residue, Gm | | Percentage of Residue | | Per- centage of Water |
|-----|----------------|--------------|-----------------------------|-------|----------------------|-------------------|-------|--------------------------|------|--------------------------------|
| | | | Moist | Dry | | Moist | Dry | Moist | Dry | |
| 2 | Banana, baked | Yes | 215 0 | 54 9 | 22 0 | 86 15 | 12 41 | 40 0 | 22 6 | 85 6 |
| 1 | Banana, baked | Yes | 150 0 | 38 3 | 22 0 | 87 76 | 11 40 | 58 5 | 29 8 | 87 1 |
| 3 | Apple, baked | No | 300 0 | 55 3 | 19 2 | 136 08 | 13 86 | 45 4 | 25 1 | 89 8 |
| 2 | Apple, baked | No | 200 0 | 36 8 | 20 2 | 101 01 | 10 86 | 50 5 | 29 5 | 89 2 |
| 1 | Apple, baked | No | 100 0 | 18 4 | 14 7 | 54 01 | 6 64 | 54 0 | 36 0 | 87 7 |
| 3 | Apple, raw | No | 300 0 | 38 1 | 19 2 | 147 10 | 17 45 | 49 0 | 45 8 | 88 1 |
| 1 | Apple, raw | No | 100 0 | 12 7 | 14 7 | 50 36 | 6 42 | 50 4 | 50 6 | 87 2 |
| 2 | Apple, raw | No | 200 0 | 25 4 | 20 2 | 118 36 | 9 67 | 59 2 | 38 0 | 91 8 |
| 3 | Butter | No | 156 0 | 140 4 | 10 0 | 95 90 | 11 15 | 61 5 | 7 9 | 88 3 |
| 2 | Butter | No | 99 0 | 89 1 | 10 0 | 72 98 | 11 35 | 73 7 | 12 7 | 84 4 |
| 3 | Prunes, pureed | No | 200 0 | 75 0 | 12 8 | 120 45 | 14 21 | 60 2 | 18 9 | 88 2 |
| 2 | Prunes, pureed | No | 200 0 | 75 0 | 20 2 | 154 65 | 18 68 | 77 3 | 24 9 | 87 9 |
| 3 | Prunes, pureed | No | 343 0 | 128 6 | 22 0 | 297 85 | 34 82 | 86 8 | 27 1 | 88 3 |
| 1 | Prunes, pureed | No | 87 0 | 32 6 | 12 8 | 79 35 | 10 44 | 91 2 | 31 9 | 86 8 |
| 2 | Prunes, pureed | No | 217 8 | 81 7 | 22 0 | 199 20 | 24 33 | 91 5 | 29 7 | 82 8 |
| 1 | Prunes, pureed | No | 150 0 | 56 3 | 22 0 | 159 36 | 17 16 | 106 2 | 30 5 | 89 2 |
| 1 | Swiss cheese | Yes | 179 8 | 116 8 | 26 4 | 171 79 | 12 87 | 95 6 | 11 0 | 92 5 |
| 2 | Potato, baked | No | 217 0 | 51 5 | 22 0 | 187 85 | 24 10 | 86 6 | 46 8 | 87 2 |
| 1 | Potato, baked | Yes | 150 0 | 35 6 | 22 0 | 140 79 | 15 76 | 93 8 | 44 3 | 88 8 |
| 3 | Potato, baked | No | 343 0 | 81 3 | 22 0 | 348 58 | 46 91 | 101 6 | 57 7 | 86 5 |
| 2 | Banana, raw | Yes | 215 0 | 44 9 | 22 0 | 211 89 | 17 48 | 98 5 | 38 9 | 91 7 |
| 1 | Banana, raw | Yes | 150 0 | 31 4 | 22 0 | 167 96 | 10 25 | 111 97 | 32 7 | 93 8 |
| 3 | Banana, raw | Yes | 310 0 | 71 1 | 22 0 | 481 01 | 40 31 | 141 4 | 56 7 | 91 6 |

Raw egg albumin is dietetically a most interesting substance. It is well known that it runs through the stomach and out of the pylorus undigested, and we found that it goes through the small bowel in the same way, in fact, in these experiments it was seen to run out of the rectum unchanged. Similar observations have been made by Bateman, who found that when he gave considerable amounts of raw white of egg to dogs, rats, rabbits and man, it caused diarrhea. It appeared to be utilized to the extent of from 50 to 70 per cent only. Even in animals with an intact colon, the feces were liquid, soft, or pasty, and contained unchanged egg-white. In a small dog, two raw eggs produced softening of the feces, while four or five produced diarrhea. They had this effect even when mixed with other foods. Dried egg-white was found to be just as indigestible as the liquid substance.

The work of Aufrecht and Simon¹⁰ suggests that raw egg is much better tolerated by man than by the dog, but their results are so divergent from ours and those of Bateman¹¹ that the subject should be further investigated. Chart 2 shows the striking differences in the digestibility of raw, soft boiled and hard boiled eggs.

The high percentage of dry residue obtained after giving lactose is of interest because this substance is supposed to be almost unabsorbable by

10 Aufrecht, S., and Simon, F. Ueber Nahrwert und Ausnutzung roher und weichgekochter Huhnereier, *Deutsche med Wchnschr* **2** 2308, 1908.

11 Bateman, W. G. The Digestibility and Utilization of Egg Proteins, *J Biol Chem* **26** 263, 1916.

the mucous membrane of the bowel. For this reason, it may increase the fluidity of the intestinal contents and act as a laxative in much the same way as does magnesium sulphate.

The highest percentage of moist residue was found with raw banana (141.4 and 111.97 per cent), and this food sometimes gave rise to stools larger than the original meal. Other foods giving stools slightly larger than the meal were prunes (106.2 per cent) and baked potato (101.6 per cent). Large moist residues were obtained also after feeding lard, butter, Swiss cheese, apple, milk, raw egg albumin and bread.

The large stools obtained with prunes and baked apple were to be expected in view of the well known laxative properties of these foods. Our experiments suggest that bananas also might be used in the treatment of patients who are constipated. Von Noorden and Salomon¹² call attention to the fact that in Germany potatoes are sometimes used for this purpose, when eaten in large quantities, they give rise to large mushy stools. It is well known also that butter and cream are slightly laxative when given in sufficient amounts.

The large residue obtained with milk is interesting because it throws light on the fact that this food is not well tolerated by many persons. After taking considerable quantities of it, many become constipated, others are troubled with diarrhea, and in both groups there are many who suffer from flatulence and "biliousness." The poor digestibility of cow's milk has been commented on by Voit, Prausnitz and many other authorities quoted by von Noorden and Salomon. The last named writers comment on the fact that milk is not so well utilized in the bowel as are eggs, meats or even some of the softer vegetables. They estimate, from experiments reported by many workers, that when milk is ingested the percentage of dry substance excreted in the stools of healthy men and women is about 7.1 per cent.

Influence of Comminution—Strange to say, when meat or liver was given in the form of lumps, the percentage excreted was a little smaller than when the food was given hashed. It must be remembered however, that the dog's digestive tract must be particularly well prepared for the handling of unchewed food.

Influence of the Amount of Food Given—One would expect the amount of moist residue to vary directly with the amount of food given, and we found this to be true. One would expect also that when the amount given exceeds that which the intestine can handle efficiently, the percentage excreted would rise rapidly. Muller noticed that in normal

¹² Von Noorden, K. H., and Salomon, Hugo. *Handbuch der Ernährungslehre*, Berlin, Julius Springer, 1920, p. 1.

dogs fed with fatty foods a certain amount could be handled satisfactorily, but when this was exceeded, the stools immediately became voluminous, foul and full of neutral oil. He apparently was unable to reach the upper limit of tolerance for meat, because, even when he gave 2,500 Gm to a dog weighing 35 Kg, digestion was a little more complete than when he gave 500 Gm. So far as our experiments went, they showed the same result, the meat was always well digested, but on some occasions we probably gave more fat than the animal could digest. More work might well have been done on this phase of the problem.

SUMMARY

The experiments here reported suggest that the best basis for a low residue diet is lean meat. To this might be added rice, hard boiled eggs, sugars (except lactose) and probably small amounts of fruit juices, tea and coffee. The highest degrees of absorption could probably be secured by giving small amounts of food several times during the day. Our experience with the dogs, together with that of Beuttenmuller¹³ with a patient with a fistula in the terminal ileum, suggests that less material will be carried into the colon if the diet is kept fairly dry.

There is considerable evidence both in the experiments here reported and in the literature to show that when it is desired to prevent bowel movements, milk should not be given. The large residue often left in the terminal ileum after the taking of milk may account for the fact that it is not well tolerated by many persons and that it makes them "bilious." This is a point that we think should be brought to the attention of the medical profession, because there is a tendency on the part of many physicians to prescribe milk and sometimes nothing but milk whenever they wish to give the digestive tract a rest. They are prone to prescribe it also in cases of diarrhea, although it appears that it is one of the first foods they should interdict. It has been our experience that milk has a bad effect on many persons with diarrhea who promptly get well when given nothing but meat or meat with a little pure starch and sugar.

It is interesting to see how closely our figures for percentage of fecal residue with different foods agree with many of those obtained on animals and man with the colon intact. It supports other observations showing that the mucous membrane of the colon absorbs little besides water.

13 Beuttenmuller, Helene. Beobachtungen an einer Zoekalfistel, Munchen med Wchnschr 1 743, 1920

Attention is called again to the peculiar indigestibility of raw egg albumin, an important point because some physicians and most laymen believe that there is nothing more nourishing than a raw egg

Curious also was the inability of the dogs to digest raw banana, Swiss cheese, baked potato and white bread. We were not surprised at their inability to digest apple, because this fruit is not tolerated by many men and women

STREPTOTHRIX NECROTIC BRONCHOPNEUMONIA *

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NEW YORK

The clinical similarity of mycotic infection of the lung to tuberculosis renders the differential diagnosis of both therapeutic and prognostic importance. Since but relatively few cases of infection by *streptothrix* as distinguished from actinomycosis, have been recognized and reported, the following record of a case seems pertinent.

REVIEW OF THE LITERATURE

Cohn¹ in 1875 first gave the name *Streptothrix foersteri* to a filamentous branched organism isolated from a lacrimal duct concretion.¹² Eppinger,² however, gave the first classic description of a case—an abscess of the brain from which a pure culture could be isolated using the ordinary mediums. He named this fungus *Cladothrix asteroides*. Further work confused this organism with the organism now known, at least generically, as *Actinomyces* (Bollinger³), which is especially characterized by the sulphur granules, clubbed ends of the filamentous mycelium and the fact that it is most commonly seen in the "lumpy jaw" infections of cattle.

In 1888, Nocard⁴ described an organism which was later termed *Streptothrix farcinica*, isolated from a disease indigenous in the Guadeloupe Islands and known as "farcin du boeuf." De Toni and Trevisan⁵ named the whole group *Nocardia* in honor of the discoverer of *Streptothrix farcinica*.

The name *Cladothrix asteroides* was changed by Rossi Doria⁶ in 1891 to *Streptothrix eppingeri*, because the false branching of *Cladothrix* was not present.

* From the service of Dr. Lewis Conner and the Pathological Department (Dr. W. Elser), Cornell Division of New York Hospital.

1 Cohn, F. Untersuchungen über Bakterien. II. Beitr. z. Biol. d. Pflanz. **1** 141, 1875.

1a Forster. Pilzmassen in unteren Thränenanalchen, Arch. f. Ophth. **15** 318, 1869. Von Graefe, A. Arch. f. Ophth. **15** 324, 1896, **1** 284, 1854.

2 Eppinger, H. Ueber eine neue, pathogene Cladothrix, Beitr. z. path. Anat. u. z. allg. Pathol. **9** 287, 1891.

3 Bollinger, O. Ueber eine neue Pilzkrankheit beim Rinde, Centralbl. f. d. med. Wissensch., 1877, p. 481, Deutsche Ztschr. f. Thiermed. **3** 334, 1877.

4 Nocard, E. Note sur la maladie des boeufs de la Guadeloupe, Ann. de l'Inst. Pasteur, 1888, vol. 2, p. 293.

5 De Toni and Trevisan. Schizomycetaceae, Saccardo—Sylloge fungorum, 1889, vol. 8.

In 1898, von Lachner-Sandoval⁷ reviewed the matter and attempted to settle it on the grounds of priority. The name *Nocardia* is antedated by both *Streptothrix* and *Actinomyces* and hence is rejected by him. The name *Streptothrix* was given by Corda⁸ to a subdivision of *Hypomycetes*, and is still in use for those fungi. By exclusion, *Actinomyces* remains as the generic name.

Thus, MacCallum and his associates use this terminology. As Wright⁹ has pointed out, however, the biologic characteristics of the organism isolated by Nocard are widely divergent from the characteristic *Actinomyces bovis* or "ray fungus." Therefore, he does not see any justification for the classification of such varied organisms as *Actinomyces bovis* and the variously named *Nocardia*, *Streptothrix*, etc., as described by Nocard and Eppinger under one heading. His belief is that usage renders the name *Streptothrix* justifiable. While this solution is certainly far from satisfactory, until more cases are carefully studied it seems best to use this classification. Hence the name *Streptothrix* is used in this paper to be synonymous with *Nocardia*, *Actinomyces asteroides*, *Streptothrix eppingeri* and *Cladothrix asteroides* following Wright's studies, as distinct from the "ray fungus" or *Actinomyces bovis*.

That the literature of the subject is greatly confused should cause little wonder. It is the denouement of an evanescent systematization.

In general, the organism shows true branching, and the ends are not clubbed, it is gram-positive. When treated with carbol fuchsin and then with Gabbett's decolorizing solution it retains the stain, and to some extent when treated with an acid alcohol (Czaplewski's reagent). It grows well on potato and agar aerobically. MacCallum,¹⁰ Steele,¹¹ Henrici and Gardner,¹² and Musgrave, Klegg and Polk¹³ give excellent descriptions of these characteristics. Wheal and Chown's staining method¹⁴ is said by Gibson¹⁵ to be useful for staining the mycelium in tissues. Feistmantel¹⁶ first carefully studied the acid fast qualities of the organism.

6 Rossi, Doria. Ann d'hist d'ig sper d' Univ di Roma **1** 4, 1891.

7 Von Lachner-Sandoval. Ueber Strahlenpilze, Inaug. Dis., Strassburg, 1898.

8 Corda, A. C. Pracht flora europaischer Schimmelbildungen. Leipzig and Dresden. 1839.

9 Wright, H. Nelson's Loose Leaf Living Medicine, 1921, vol. 2, p. 364.

10 MacCallum, W. G. Centralbl f Bakteriöl **31** 629, 1902.

11 Steele, A. E. A Streptothrix Organism from a Brain Abscess, J. M. Research **44** 305, 1923-1924.

12 Henrici, A. T. and Gardner, E. L. The Acid Fast Actinomycetes, J. Infect. Dis. **28** 232, 1921.

13 Musgrave, Klegg and Polk. Philippine J. Sc. **3** 447, 1908.

14 Wheal and Chown. J. Path. & Bact. **16** 146, 1911.

(Footnotes continued on following page)

Many authors have contended, probably justifiably, that there are many transitional forms among this group of organisms. It may well be that the organisms are allotopic, but until such changes in state can be correlated with environment, it would seem better to describe, without attempt to distort the picture by forcing a doubtful classification,

Clinically *Streptothrix* does not show the rather specific predilections shown by *Actinomyces*. *Streptothrix* exhibits the most diverse types of infection, that of the lung probably being the most common. Isolation and identification of the organism seems the only reliable diagnostic criterion.

As far as I have been able to determine the following authors have described cases of streptothricosis: Frankel and Schottmuller,¹⁷ Almquist,¹⁸ Gasperini,¹⁹ Sauvageau and Radais,²⁰ Sabrazis and Riviere,²¹ Ferre and Faquet,²² Scheele and Petruschky,²³ Buchholtz,²⁴ Ruge,²⁵ Rullmann,²⁶ Berestnew,²⁷ Maresch,²⁸ Flexner,²⁹ Chiari,³⁰ Norris and

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16 Feistmantel, C. *Centralbl f Bakteriöl* **31** 433, 1902

17 Frankel, B. Gutartige Mykose des Pharynx, *Berl klin Wchnschr*, 1873, no 8. Schottmuller and Frankel. Ueber Streptotrichosis hominis, *Munchen med Wchnschr* **59** 1405, 1912

18 Almquist, E. Untersuchungen ueber einige Bacteriengattungen mit Mycelien, *Ztschr f Hyg u Infectiouskrankh* **8** 189, 1890

19 Gasperini, G. Recherches morphologiques et biologiques sur un micro-organisme de l'atmosphère, le *Streptothrix foersteri* Cohn, *Ann de microg*, 1890, p 449

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21 Sabrazis and Riviere. Sur un *Streptothrix* recoutre dans un cas d'abcès du cerveau et d'infarctus suppure du rien, *Presse méd*, September 22, 1894, Le parasites du genre *Streptothrix* dans la pathologie humaine, *Semaine med* **44** 383, 1895

22 Ferre and Faquet. *Semaine med*, 1895, p 359, *Mercredi med*, 1895, p 441, quoted by Flexner. *J Exper Med* **3** 435, 1898

23 Scheele and Petruschky. Culturen und Preparate einer menschen-pathogenen *Strptothrix*—Art, *Cong f inn Med* **15** 550, 1897, *Munchen med Wchnschr* **44** 686, 1897

24 Buchholtz, H. Ueber menschenpathogene *Streptothrix*, *Ztschr f Hyg u Infectiouskrankh* **24** 470, 1897

25 Ruge, H. Ueber *Actinomyces*—ahnliche Gebilde in den Tonsillen, *Ztschr f klin Med* **30** 529, 1896

26 Rullmann, W. Ueber eine aus Sputum isolirte pathogene *Streptothrix*, *Munchen med Wchnschr* **45** 919, 1898

27 Berestnew. *Ztschr f Hyg u Infectiouskrankh* **29** 94, 1898

28 Maresch, R. *Streptothrix pericarditis*, *Wien klin Wchnschr* **20** 1557, 1907

29 Flexner, S. Pseudo-Tuberculosis Hominis *Streptothricha*, *J Exper Med* **3** 435, 1898

30 Chiari, H. Ueber Myelitis suppurativa bei Bronchiektasie, *Ztschr f Heilk* **21** 351, 1900

Larkin,¹ Aoyama and Miyamoto,³² Birt and Leishman,³³ Trolldeiner,³¹ Horst,³ Engelhardt and Lohlein,³⁶ MacDonald,³⁷ Stokes,³⁸ Schbad,³⁹ Tuttle,⁴⁰ Butterfield,⁴¹ Bridge,⁴² Potron and Thery,⁴³ Steele and Lee,⁴⁴ Gibson,¹⁷ Davis and Garcia,⁴⁵ Pijper,⁴⁶ Christopherson and Archibald,⁴⁷ Finch and Jessup,⁴⁸ Evans,⁴⁹ Guy,⁵⁰ Glaser and Hart,⁵¹ Lenchaitz,⁵² Henrici and Gardner,⁵³ Iacono,⁵⁴ Callender,⁵⁵ Gougeot⁵⁶ and Levy⁵⁷

31 Norris, C., and Larkin, J. H. Two Cases of Necrotic Broncho-Pneumonia with Streptothrix, *J. Exper. Med.* **5** 155, 1900

32 Aoyama and Miyamoto. Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo **4** 231, 1900

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43 Potron, M., and Thery, G. Pyodermatomyose provoquée par un "Nocardia", *Rev. med. de l'est* **45** 159 and 198, 1913

44 Steele and Lee, R. I. A Case of Infection with Nocardia, *Boston M. & S. J.* **169** 502, 1913 footnote 11

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46 Pijper, A. Nocardiosis—Case of Bronchitis from Nocardia, *M. J. S. Africa* **12** 141 1916-1917

47 Christopherson, J. B., and Archibald, R. G. Primary Nocardiosis of the Lacrimal Gland. *Lancet* **2** 847, 1918

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(Footnotes continued on following page)

REPORT OF A CASE

History—An Irish chauffeur, aged 41, complained of hemoptysis for eight months, without associated pain in the chest. During childhood, he had measles and whooping cough. Thirteen months before admission, the patient had a rather severe lobar pneumonia on the right side, and three months later a productive cough developed and persisted. A month later, he began suddenly to have a severe pain in the right side of the chest, associated with slight fever and a more violent cough. Within two or three days, the pain ceased, but the cough persisted. The patient then noticed streaks of blood in the sputum which had formerly been yellow. Four months later, a sudden severe hemorrhage occurred, with the loss of a pint or more of blood. It was believed at another hospital that he had an abscess of the lung. After a nine weeks' stay at the hospital, the patient had recovered sufficiently to return to work. One year after the onset of his trouble he had another severe hemorrhage which caused his admission to the New York Hospital. During his stay, a continuous hemoptysis was in progress. After two days in the hospital he had another severe hemorrhage during which he died.

Physical Examination—The patient was well developed but showed a slight loss of weight (the average weight was 180 pounds [81.6 Kg] and the present weight 160 pounds [72.6 Kg]), rested comfortably, was slightly dyspneic and sweated profusely. The mucous membranes and nail beds were dusky and cyanotic.

The respiration was fast and shallow. Expansion was about equal on both sides. The heart apex was in the fifth interspace, 11 cm. from the midline, the rate was 130 beats per minute and the action was regular without any abnormal sounds. The resonance was definitely impaired over the anterior lower two thirds of the right side of the chest. The breath sounds had a poor vesicular quality especially anteriorly over the right side of the chest. The voice sounds were unchanged. A few scattered râles were heard, especially in the right axilla. A friction rub was heard in the right posterior axillary line toward the lower lobe. Unfortunately, the chest could not be given a thorough examination, because of the almost continuous hemoptysis.

An indefinite superficial mass was felt in the upper left quadrant of the abdomen, with associated spasm and tenderness.

The nails were rather markedly clubbed. The examination otherwise did not reveal any thing pertinent.

The temperature was variable, with sharp drops and raises ranging from 100 to 105 F. The pulse rate closely paralleled the variations of the temperature. The respiration averaged 44 breaths per minute. The blood pressure was 115 systolic and 87 diastolic.

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Laboratory Examination—The red blood cells numbered 4,880,000, the white blood cells numbered 11,200 (78 per cent neutrophils, 19 per cent lymphocytes, 3 per cent mononuclears) and the hemoglobin content was 70 per cent. The Wassermann reaction was negative. The urine showed a marked trace of albumin and sugar and an occasional hyaline cast. The blood urea nitrogen was 17.4 mg per hundred cubic centimeters.

The sputum was profuse, had a foul fecal odor and was blood stained and watery. Acid fast bacilli were not found on repeated examination. One clump of irregularly thickened branching gram-positive organisms were found.

Autopsy—The heart weighed 330 Gm, but was of normal size and shape. On the anterior surface of the right ventricle about 1 cm from the tricuspid valve was a small cavity 4 mm in diameter filled with greenish yellow purulent material. The endocardium, valves and coronary vessels were normal. A round mass similar to a thrombus was seen lying in the lumen of the right ventricle. The center of this mass was occupied by *Streptothrix*. The pericardial cavity contained a moderate amount of turbid serous fluid.

The right lung weighed 1,075 Gm. Scattered over the surface were numerous deep grayish-blue areas in which yellow patches were seen. These areas appeared to be consolidated. On section, the larger part of the cut surface was found to be occupied by grayish granular consolidated masses which in most instances showed central necrosis. At numerous places in these masses of consolidation were central cavities filled with greenish-black, foul smelling material. Other masses presented innumerable small yellowish-gray foci scattered through a reddish-gray consolidated matrix. These lesions were most advanced in the lower lobe. The upper part of the lower lobe contained a cavity about the size of a walnut; the inner surface was deep red and at one place a medium sized vessel was eroded. This erosion may reasonably be assumed to represent the source of the hemoptysis. The cavity communicated with a bronchus. The mucosa of the bronchus was deeply injected and covered with a grayish-brown mucoid material. The left lung weighed 675 Gm. Lesions similar to those in the right lung but not so advanced were present throughout the left lung.

The peritoneal cavity did not contain an excess of fluid. Opposite the umbilicus and about 10 cm to the left of the midline, the parietal peritoneum showed an indistinctly circumscribed bluish-red discoloration. In the wall of this region a large abscess filled with thin brownish-gray material was found. This purulent material extended into the neighboring muscles forming fistulous tracts extending from the costal margin to the inguinal ligament.

The liver weighed 2,425 Gm; it was normal in shape. On section, the normal markings were distinct. There was some passive congestion. The biliary system was apparently normal.

The spleen weighed 250 Gm; was very soft and the normal markings on section were found to be obscure. The larger part of the cut surface was of a pale pink color alternating with deep red areas apparently the seat of large hemorrhages.

The gastro-intestinal tract and the pancreas were normal.

The left kidney weighed 250 Gm; the right 200 Gm. Nothing of importance was found in the examination of the kidneys. The pelvis and ureters did not show any gross lesions. The bladder and genitals were normal.

The aorta showed moderate sclerosis.

Histologic Examination.—The abscess showed the central grayish-blue granular masses of *Streptothrix* surrounded by a zone of marked infiltration with poly-

morphonuclear leukocytes and plasma cells and rather extensive necrosis of the myocardium surrounding the cavity. Some of the muscle cells were filled with fat. This abscess is shown in figure 1.

Histologically, the yellowish-gray foci were found to represent abscesses in the lungs, showing a central, finely granular, grayish-blue mass, surrounded by a diffuse plasma and invasion by polymorphonuclear leukocytes. The walls of the blood vessels were often involved in the cellular exudation thus leading one to suspect that they might have been involved in the genesis of infected thrombi.

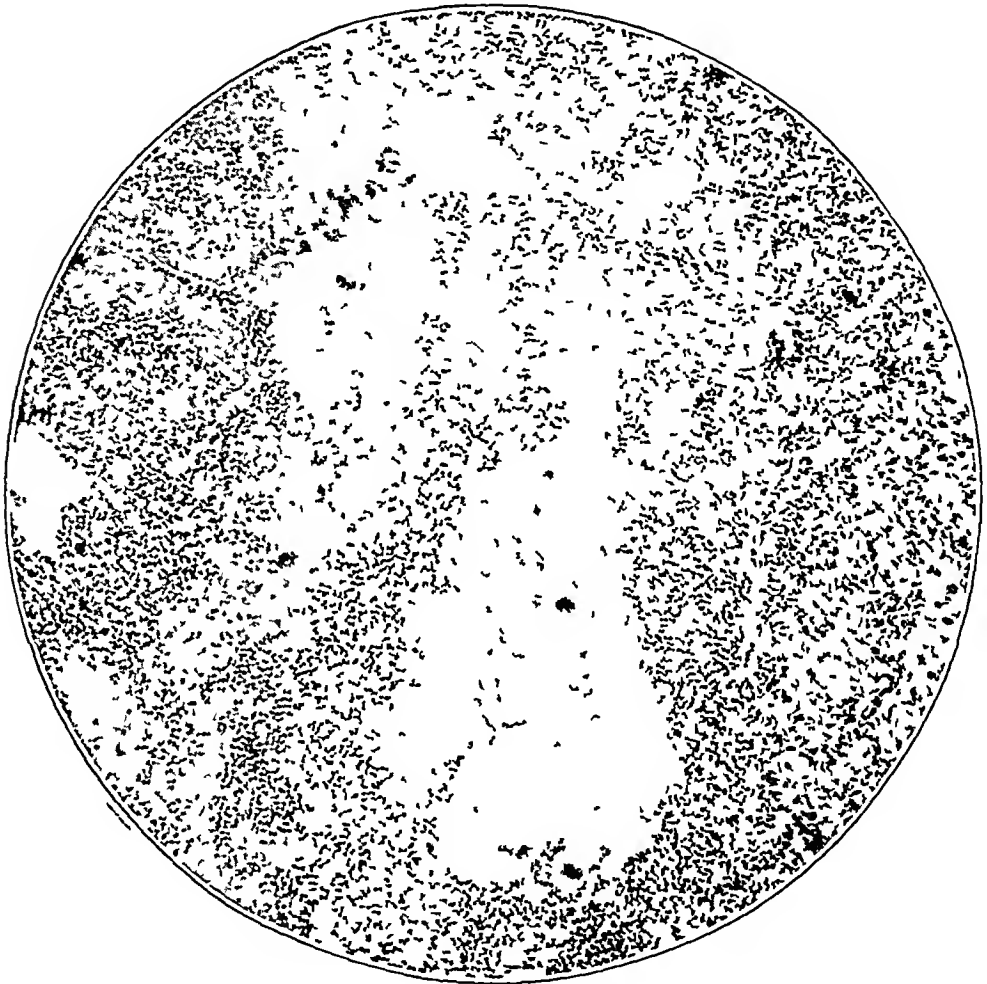


Fig 1—Abscess of the myocardium caused by *Streptothrix*, which is seen as dense matted material in the center surrounded and infiltrated with polymorphonuclear leukocytes and plasma cells.

The bluish granular mass was gram-positive and was identified by culture as *Streptothrix*. At numerous places small bronchioles were found to contain a marked cellular exudate with the central bluish granular mass of *Streptothrix*. One vessel contained a mural thrombus. In large areas the alveoli were filled with blood and in some places the resulting picture was that of hemorrhagic infarction. In certain portions the alveoli were filled with a homogenous pink staining material. Areas of consolidation with exudation of polymorphonuclear leukocytes and fibrin were present. The red and white blood cells were for the most part well preserved. Figure 2 shows one of the areas invaded by *Streptothrix*.

Except for the abscess in the abdominal wall, which was almost identical in structure with those described in the myocardium the histologic examination did not reveal more of importance

Bacteriology—The organism was isolated on 2 per cent glucose agar. Branching hyphae with tapering ends were seen in such cultures. The organism was partially acid-fast and was gram-positive. Unfortunately, injections into animals were not made. The classification and isolation were carried out by Dr. Wheeler. Figure 3 shows the gram-stained *Streptothrix* in the myocardium.

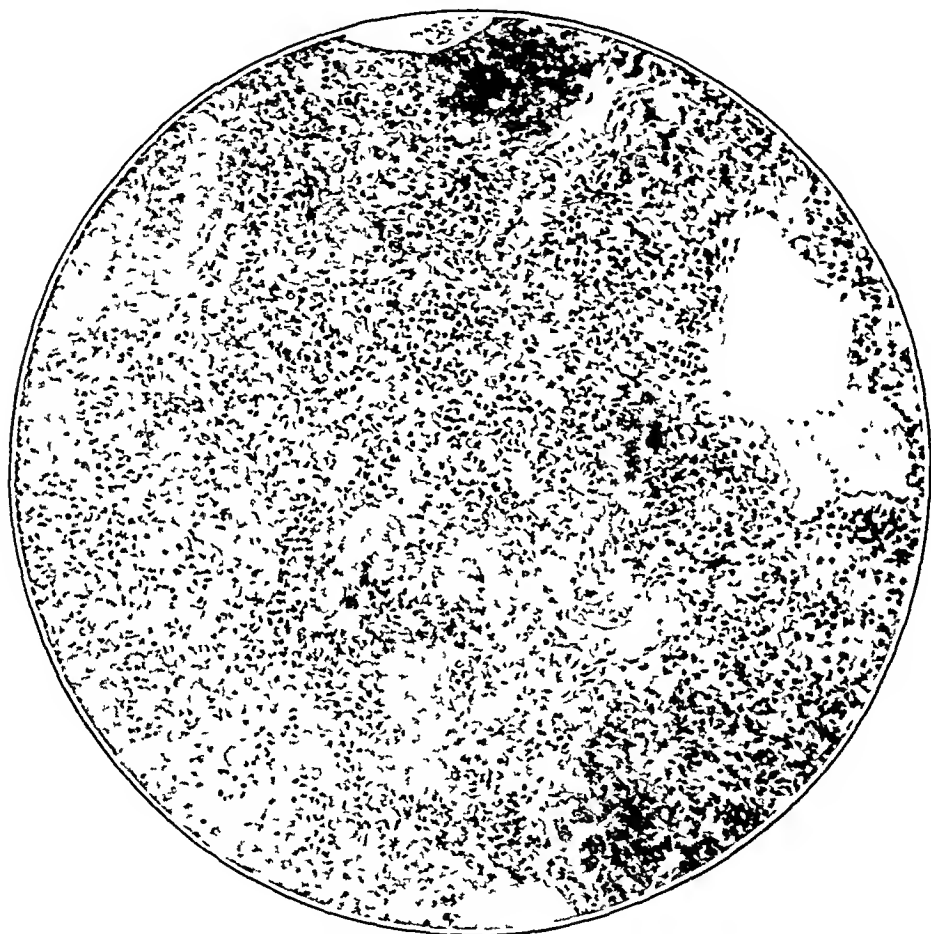


Fig. 2—Abscess of the lung caused by *Streptothrix*. The dense, deeply stained material is *Streptothrix*.

COMMENT

Though streptothricosis closely simulated tuberculosis clinically, there was little in the gross or microscopic changes to cause confusion. As in most cases of this disease nothing was ascertained concerning the manner in which the infection was obtained. Clinically one was impressed in this case with the relatively acute course associated with an almost continuous hemoptysis. Pathologically the condition was both aggressive and progressive, and it was characterized by the production of mycotic abscesses from which arose metastases. These abscesses appeared to be invasive locally by direct extension.

Streptothrix asserts itself in the most protean form and the most varied locations—at times in the brain, at times in the lung and again in the peritoneal cavity. Hence, the symptoms depend on the location of the infection. In general, however, they consist of suppuration and inflammation. The localized formation of an abscess is the rule. Metastatic abscesses often occur in diverse parts of the body—the myo-

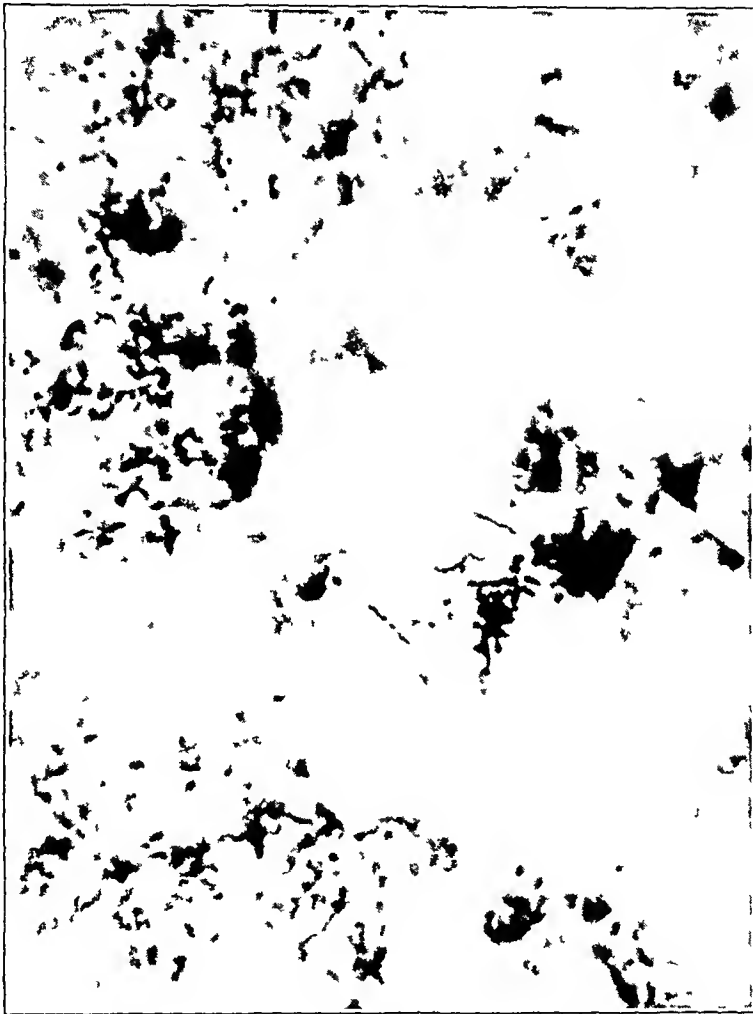


Fig. 3—Gram stain of *Streptothrix*, as seen in the myocardium, $\times 1680$

cardium, the abdomen and the walls of the chest are common sites. The infection seems to be subacute or acute more often than chronic. The pulmonary cases usually simulate tuberculosis or pneumonia with either abscess or empyema. In the brain, the symptoms and signs are those of tumor or abscess.

The conditions from which *Streptothrix* infection must be commonly differentiated are tuberculosis, pneumonia meningitis, actinomycosis, gumma and glanders. The only reasonably certain method of differentiation is the isolation and culture of *Streptothrix*, and its classification as to morphology, cultural characters and staining reactions, and usually its pathogenicity in guinea-pigs or rabbits.

Streptothrix infections offer difficulties for both the patient and the physician. The prognosis seems to be grave in the majority of cases.

Treatment with potassium iodide and autogenous vaccines has been tried with little success. The treatment so far is symptomatic with the application of such surgical and medical procedures as are indicated by the location and the extent of the disease.

Book Reviews

INNERE SEKRETION IHRE PHYSIOLOGIE, PATHOLOGIE UND KLINIK VON DR
JULIUS BAUER Price, 39 marks Pp 479, with index and 56 illustrations
Berlin Julius Springer, 1927

Dr Bauer intended this monograph on endocrinology to be different from the usual monographs, and he has in part succeeded. In the preface he admits the present plethora of monographs on internal secretion, but despite their number, easy reference is still made to endocrine causes of almost all unknown or unexplained clinical symptoms and, as Dr Bauer remarks, when disease of one endocrine organ does not seem sufficient to explain the phenomenon, the pluriglandular explanation, or direct disturbances due to lack of balance between the different endocrine glands is employed.

The author's point of view is made clear by the following quotation from the preface "If we are to arrive at a true understanding not only of the interrelations of the endocrine organs but of the relation of the endocrine organs to normal and pathological processes, we must study these organs, not alone from the point of view of experimental physiology and pathological anatomy, but also from the point of view of more general biological correlations. We must consider their relation to the individual personality, to the individual constitution and to the geno-type. Many disturbances of the internal secretion are not, as most investigators seem to assume today, the cause of pathological processes which we observe in patients, but they are themselves consequences of wider disturbances of a general type, that is, disturbances that may be called primary anomalies of the constitution. Without thorough understanding of 'constitution-pathologie,' and the facts and theories of heredity real understanding of endocrinology is impossible." This point of view is maintained throughout the monograph and particularly in the last chapter which is entitled "The Relation of Internal Secretion to the Pathology of the Organism as a Whole as well as to the Pathology of Special Organs," and in the final supplement entitled "The Relation of the Internal Secretions to the Constitutional Habitus of Man."

The monograph is to be regarded as a serious contribution to medical science. There is undoubtedly an important element of truth in the author's point of view, but at present one may question whether the introduction of such concepts as geno-type, personality and heredity without further analysis of the mechanisms of these processes does not contribute more fog than clarity to an already difficult field. The author shows familiarity both with the experimental and clinical literature, and, in most cases, good critical judgment in the evaluation of this literature. For example, he says (page 183) "Organotherapy by mouth has so far proved successful only in the case of the thyroid gland." All experimentalists and critical practitioners will agree to that statement. One is therefore greatly disappointed on turning a few pages to find that the author apparently accepts as proved the idea that the activity of such glands as the ovaries, testes and hypophysis can be increased by diathermy, that with increased protein in the diet the secretion of the thyroid can be increased, that by the nonspecific protein therapy the activity of a number of the endocrine glands can be increased, that by sexual intercourse the hypoplastic ovaries in women can be improved, and that by the roentgen ray the activity of the ovaries and the hypophysis can be increased. All of these claims have been made on the basis of experimental or clinical observations, they have also been contradicted by equally good men, none of these claims are proved, and some of them are almost disproved.

The author gives abundant references to the literature in all the chapters, but, curiously, in a short list of larger works on the endocrines at the end

of the work, the author cites thirty German publications, but only two Italian, one English, one French and two American workers. This may be all right in a book intended primarily for German biologists and clinicians, but it does not give a fair impression of the available and valuable monographs in the different languages. On page 184, the author says "Up till the present it has not been possible to control or prevent the symptoms that follow impairment of the hypophysis, the ovaries, the testes or the adrenals through any method of organotherapy." This statement has to be corrected in the case of the anterior lobe of the hypophysis for Smith and Evans have recently shown that daily parenteral administration of fresh anterior lobe of the hypophysis is able to overcome the symptoms of removing of the anterior lobe.

The present monograph will take its place with the best and the most suggestive, if not the most critical and conclusive in the field, in so far as it is possible for one man to write a standard work on this subject today.

AVITAMINOSEN UND VERWANDTE KRANKHEITSZUSTÄNDE. Herausgegeben von W. STEPP and P. GYORGY. Pp 817, with index, and 194 illustrations. Berlin Julius Springer, 1927.

This extensive monograph is the joint work of nine authors, the greater part of the work, however, being contributed by Dr Stepp and Breslau and Dr Gyorgy of Heidelberg. In the preface the editors remark that previous monographs on diseases resulting from vitamin deficiency have been written mainly by laboratory men and thus give primarily the points of view of the experimental physiologists and pathologists. The present volume is intended to supplement previous efforts in that the material is presented and discussed essentially by clinicians, and mainly on the basis of clinical material. Nevertheless, the first 200 pages of the book deals primarily with experimental avitaminosis. These 200 pages are contributed by Dr Stepp of Breslau, who writes on the physiologic side, and Dr Kühn of Erlangen, who discusses the pathologic anatomy of avitaminosis. The chapters by Dr Stepp are on the whole excellent summaries. The same cannot be said of the chapters by Dr Kühn on the pathologic anatomy of experimental avitaminosis. As an example, the author's broad statement on page 162 regarding the pathologic anatomy of the alimentary canal in experimental avitaminosis—"The entire gastro-intestinal system shows the same changes, namely, extreme atrophy with tendency to necrosis of the mucosa." "The intestinal rate is much decreased, the feces are held back, become concentrated and hard as stone."

"In all cases of experimental avitaminosis the alimentary tract becomes extremely atrophic." These are unwarranted and extreme statements. Such degree of pathology is not apparent, at least in the beginning of definite diseases resulting from vitamin deficiency in such animals as the dog, rat or pigeon.

Then follows a series of seven chapters by Dr Gyorgy of Heidelberg on Xerophthalmia, infantile tetany, osteomalacia, idiopathic tetany, scurvy, alimentary anemia in infants, and on the relation of vitamins to growth. These subjects are treated on the whole in an excellent and critical manner. Dr Gyorgy reaches the conclusion that infantile tetany is closely related to rickets and is primarily due to a deficiency of vitamin D rather than to any deficiency of the parathyroid glands. He reaches the same conclusion regarding the etiology of osteomalacia and idiopathic tetany in adults. There is a short chapter by Dr Salle of Berlin on scurvy in adults, a short chapter by Dr Nocht of Hamburg on the so-called ship beriberi, and short chapters on hunger edema by Dr Shittenhelm of Kiel, and on scurvy by Dr Fischer of Rostock. The rest of the book comprises excellent chapters on beriberi by Dr Shimazono of Tokyo, and on pellagra by Dr Lavinder of New York.

A monograph of this size and varied authorship necessarily contains errors both of omission and commission. For example, in the lengthy chapter on hunger edema by Shittenhelm (51 pages), the author leans toward the view that avitaminosis is the primary cause of the disease, and he seems not to be

familiar with the work of Dr Kohman which shows that low protein in the diet is the essential cause of the malady. Nevertheless, the work must be regarded as a serious and, on the whole, successful effort to summarize our present knowledge of the diseases caused by vitamin deficiency for the aid and direction of the practicing physician. Every internist who is capable of handling German may pursue the monograph with profit.

INTRODUCTION TO THE STUDY OF EXPERIMENTAL MEDICINE. By CLAUDE BERNARD (Translated under the auspices of the General Educational Board, by Henry Copley Green, A.M.), introduction by Laurence J. Henderson. New York: The MacMillan Company, 1927.

The translation of the book has rendered a real service to medicine by making it available to English readers. The subject is one in which Claude Bernard is deeply interested. His firm belief that the advancement of medicine was to be made in the laboratory is evident throughout. Time has shown the correctness of his prediction.

It is impossible in a review to give an adequate conception of the significance of the subject matter contained in this book. Perhaps a better insight may be acquired by making some quotations.

In his discussion of the difference and interrelation between observation and experiment, he accepts Cuvier's distinction. "The observer listens to nature, the experimenter questions and forces her to unveil herself."

"The art of investigation is the corner stone of all experimental science."

"In the experimental sciences all progress is measured by improvement in the means of investigation."

"Experiment is an observation induced with the object of bringing to birth an idea."

"We must observe without any preconceived idea, the observer's mind must be passive, that is, it must hold its peace, it listens to nature and writes at nature's dictation."

"The results of an experiment must be noted by a mind stripped of hypothesis and preconceived ideas."

"We must never make an experiment to confirm our ideas but simply to control them."

"Genius is revealed in a delicate feeling which correctly foresees the laws of natural phenomena, but this we must never forget, that correctness of feeling and fertility of idea can be established and proved only by experiment."

Dr Henderson's introduction is in full accord with the spirit of the book. This volume can be read with profit by every active or prospective investigator in medicine.

THE NORMAL CHEST. By DR J. A. MYERS. Price, \$3.50. Baltimore: Williams & Wilkins Company, 1927.

This is, so far as I know, the first satisfactory book on the normal chest. Writers and teachers have usually avoided the subject for the excellent reason that it is almost impossible to interest students in it. In order to maintain interest one must write and teach about the normal and the abnormal chest in "their" contrasts with each other. That is just what this book does, and thereby it maintains interest. Some of the topics mentioned, despite the fact that they do not exist in the normal chest, are plural and pericardial adhesions, anemia, aneurysm, angina pectoris, arrhythmia, arteriosclerosis, hypertension, cavernous breathing, cardiac dilatation, convulsions, cyanosis, D'Espine's sign, ectopia cordis, emphysema, fibrillation, Flint's murmur, foreign bodies, friction sounds, exophthalmic goiter, heart block, heart murmurs, Hodgkin's disease, kidney disease, migraine, mitral stenosis, pectoriloquy, pericardial effusion, pleurisy, pneumonia, pneumonothorax, râles (thirteen references), rickets, sarcoma, syncope, syphilis, tuberculosis (nineteen references) and many others.

With this wholly sensible admixture of the diseases of the normal and the abnormal chest, one can make an interesting and helpful book as Dr Myers and his collaborators have done.

Among the most valuable chapters are those on the acoustics of auricular fibrillation and percussion, on the developmental anatomy of the chest and the roentgenogram of the normal chest.

Minor points with which I am not in agreement are the references to emphysema (a disease which has not as yet any known physical signs whereby it can be distinguished from the conditions existing in the "barrel chest without emphysema") the remarks about "impure heart sounds" on page 148 and the sections on that useless survival, cardiac percussion.

But as a whole, the book is excellent and it may be confidently recommended to teachers and students of disease of the chest.

DISEASES OF THE DIGESTIVE ORGANS WITH SPECIAL REFERENCE TO THEIR DIAGNOSIS AND TREATMENT By CHARLES D. AARON, Sc.D., M.D. Fourth edition, thoroughly revised. Price, \$11. Pp. 927 with 174 engravings, 70 roentgenograms and 13 colored plates. Philadelphia: Lea & Febiger, 1927.

On the whole the book is well outlined and complete. The chapters on laboratory tests and analyses are good. The authors' statements concerning the indications for duodenal lavage (114 pages) and its therapeutic results, and intestinal toxemia (chapter XXXIX) however, are not generally accepted. The chapters on acute and chronic gastritis (XXII and XXIII) and gastroenteroptosis and the symptomatology attached thereto seem a bit overemphasized in the light of present knowledge.

THE SYNDROME OF MALIGNANT HYPERTENSION

NORMAN M KEITH, M D

HENRY P WAGENER, M D

AND

JAMES W KERNOHAN, M B

ROCHESTER, MINN

Three years ago, two of us (H P W and N M K) ¹ reported a series of cases of characteristic retinitis associated with marked hypertension and adequate renal function. The history and clinical data differed from those usually noted in cases of chronic nephritis. We then pointed out the serious prognostic import of this typical retinitis. The term "malignant hypertension" was applied to this clinical condition, apparently correctly, because in all of the fourteen cases so diagnosed, death occurred within from one to forty-four months. Since then we have seen a large number of similar cases, in some of which moderate renal insufficiency had developed. In the present communication, we wish to present the observations in eighty-one cases. Forms of severe hypertension without this retinal picture, while recognized as potentially malignant, are not included in this series. Further data have been collected which show that this condition may occur even in childhood and that it may be superimposed on previous general arteriosclerosis and on benign hypertension. We wish to emphasize that many of these patients were up and about and generally did not complain of severe discomfort, and yet the retinal changes warned the physician of the seriousness of the general pathologic process. Detailed studies of the cardiovascular system have been made with special emphasis on the disturbances of retinal, cerebral, cardiac and renal functions. The relative impairment of the functions of these various organs differed but, when correlated, indicated the widespread effects of the disease process. In this paper, our object is to show the relationship of certain apparently isolated signs and symptoms to a definite clinical and pathologic syndrome.

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1 Wagner, H P, and Keith, N M. Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, Arch Int Med **34** 374 (Sept) 1924

CLINICAL SYNDROME AND PHYSICAL MANIFESTATIONS

Forty-eight of the eighty-one patients were males and thirty-three, females. The ages ranged from 9 to 64 years, the average being 42, but the majority of the patients were between 33 and 55 (fig 1). This age incidence is similar to that reported by Fahr² in cases of malignant sclerosis. On examination, patients reported the onset of symptoms from one month to six years previously. These were naturally diverse, headache, general weakness and nervousness were the most common. Visual disturbances were reported in forty-three cases. Symptoms arising from actual organic lesions of the central nervous system were present in twenty-nine cases. In five cases, the history and examination

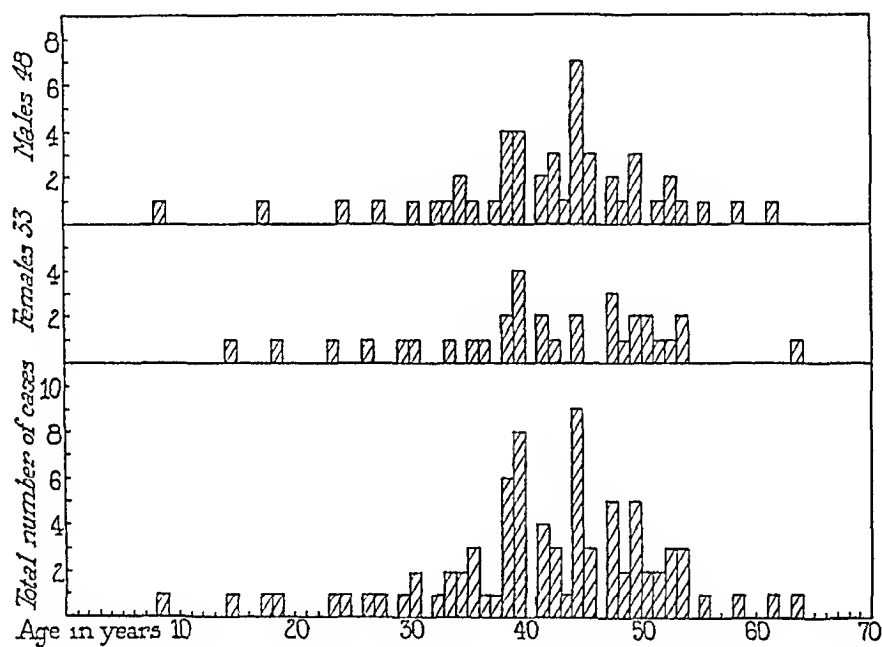


Fig 1—Age incidence

suggested tumor of the brain³. When general convulsions occurred, the patient was usually less than 40, while hemiplegia was most common in those more than 40. Loss of weight and strength was striking in nine-

2 Fahr, T. Nephrosclerosis, *Deutsche Arch f klin Med* **134** 366, 1920

3 Wagener and Woltman have found that the pressure of the cerebrospinal fluid was increased above the normal in several of these cases and that drainage by lumbar puncture temporarily relieved certain cerebral symptoms. The increased pressure of the spinal fluid in cases of hypertension has been mentioned previously by Volhard and Fahr (*Die doppelseitigen hamatogen Nieren erkrankungen*, Berlin, Julius Springer, 1918). *Die Brightsche Nierenkrankheit* Klinik, Pathologie und Atlas, Berlin, Julius Springer, 1914. Bailhart, Magniel and Saragea (*Mesures de la pression arterielle retinienne et de la tension cephalo-rachidienne dans quelques cas d'hypertension arterielle*, *Arch d mal du coeur* **17** 289, 1924) and Block and Oppenheimer (*A Comparative Study of Intraspinal Pressure, Blood Pressure and Intra-Ocular Tension*, *Arch Neurol & Psychiat* **11** 444 [April] 1924).

teen cases, a loss of 75 pounds (34 Kg) in six months occurred in one case. There was a previous record of definite hypertension in forty-eight cases. This had been known to the patients for varying periods of from a few weeks to ten years. In forty-nine cases there was a history of dyspnea on exertion or of transient dependent edema. The patients rarely complained of urinary symptoms, which usually consisted of slight or moderate nocturia. In one patient who was under observation for ten years, a trace of albumin was usually present in the urine. Albumin and casts had been known to be present previously in many cases, the history in one dating back seven years. Uremic manifestations were extremely rare, and when coma occurred during the terminal picture, it was not typical of uremic states.

The general physical examination was particularly directed to the cardiovascular system. Clinical evidence of anemia was almost always absent. On account of certain symptoms of hypersensitiveness and nervousness, the thyroid gland was always palpated, but diffuse or nodular enlargements were infrequent. Evidence of paralysis was sought. Paralysis of single nerves was rare, that of the facial nerve occurring twice and of the abducens, once. Our criteria as to the extent of peripheral arteriosclerosis and sclerosis of the arterioles⁴ were the appearance of the temporal and retinal arteries and the palpable condition of the radial and brachial arteries. The grade of sclerosis in the retinal arterioles, as evidenced by the degree of constriction and irregularity in caliber, varied from mild to severe. The sclerosis was marked in thirty-three cases. In nine of these, the high degree of visible sclerosis was caused in part by the associated retinitis. The amount of peripheral sclerosis varied from slight to extreme. Marked sclerosis occurred in nineteen cases. Evidence of arterial thrombosis or embolism in the limbs was not encountered. In thirty-one cases there were objective symptoms of cardiac decompensation, the symptoms were mild in twenty-two and severe in nine. Measurable cardiac enlargement was noted in many cases, although in sixteen, distinct enlargement could not be demonstrated and in forty it was slight. Extreme grades of enlargement were demonstrable in only six cases.

On auscultation, accentuation of the second aortic sound was observed in sixty-seven cases and was the most usual abnormal observation. Cardiac murmurs occurred in thirty-three cases, in twenty-one of these the murmur was systolic in time and was heard most clearly over the base of the aorta, in nine cases, an apical systolic murmur was heard, in only three was there an aortic diastolic murmur. In one case there was serious disturbance of cardiac rhythm, auricular fibrillation being present.

4 These terms are used in general throughout the paper, although it will be shown that, while varying degrees of sclerosis were found in some of the arteries, the condition in the arterioles is described more accurately by the term hypertrophy.

TABLE 1—Clinical Data on Admission

| Case No. | Age and Sex | Date of Admission | History of Present Illness | Second Aortic Sound, Pericardial Area | | Weight, Kg | Heart, Grade | Lungs, Grade | Spleen, Grade | Blood Pressure | | | | Retinal Changes | | Date of Death | Duration of Life from First Admission, Months | Comment |
|----------|-------------|---------------------|--|---------------------------------------|-------|------------|--------------|--------------|---------------|----------------|------------|-----------|--------------------------|-----------------|-------|---------------|---|---------------------------|
| | | | | Size of Aorta | Sound | | | | | Admission | Dismission | Retinitis | Arterio sclerosis, Grade | | | | | |
| | | | | | | | | | | | | | | Sys | Diast | | | |
| 1 | 52 Q | 2/28/24 | From 2 to 3 years, headache, dyspnea, dysarthria, visual disturbances, blood pressure systolic 190, diastolic 90 | 1 | 2 | 1 | 1 | 1 | 250 | 160 | 210 | 135 | 2 | 3 | 3 | 1/9/25 | 10 | |
| 2 | 42 Q | 6/20/25 | Headache, 1 1/2 years, hypertension, 2 years, purpura, 1 year, visual disturbances, 2 weeks | Normal | 1 | 3 | | | 265 | 165 | 240 | 160 | 2 | 2 | 2 | May, 1925 | 11 | |
| 3 | 46 Q | 11/21/22 1/20/25 | Albuminuria and cylindruria, 7 years, hypertension, 1 year, headache, 6 months | 1 | 1 | 1-2 | | | 220 | 110 | 150 | 90 | 1 | 2 | 2 | 7/22/26 | 14 | Right hemiplegia |
| 4 | 50 Q | 6/19/21 | Nervousness and dyspnea, 2 years, visual disturbances, 3 weeks, loss of weight | 1 | | | | | 280 | 170 | 285 | 160 | 2 | 1 | 2 | 5/15/25 | 11 | |
| 5 | 40 Q | 9/23/21 | Severe headache, 3 years, hypertension, 1 year, pericardic edema of ankles | 1 | 1 | 2 | | | 235 | 150 | 170 | 110 | 1 | 2 | 3 | Jan, 1923 | 16 | |
| 6 | 53 Q | 1/31/24 | Dyspnea, 9 months, dependent edema, 3 months, epistaxis, 3 weeks | 1 | 1 | 1 | 1 | 1 | 240 | 175 | 205 | 100 | 2 | 3 | 3-4 | 12/ 1/24 | 10 | |
| 7 | 25 Q | 10/21/21 | Headache, loss of vision, loss of weight for 20 months, epilepsy, 18 months | Normal | 1 | 1 | | | 240 | 165 | 190 | 130 | 3 | 4 | 4 | 12/31/21 | 2 | Question of tumor cerebri |
| 8 | 45 Q | 8/26/26 | Hypertension and severe headache, 5 years, visual disturbances, 1 month | 1 | 1 | 2 | | | 230 | 120 | 200 | 120 | 1 | 1-2 | 3 | 1/16/27 | 4 5 | |
| 9 | 48 Q | 5/26/25 | Headaches, 7 years, visual disturbances, 3 years, weakness, 2 months | 1 | | 3 | | | 235 | 165 | 210 | 145 | 2 | 1 | 2 | 7/ 2/25 | 1 | |
| 10 | 48 Q | 7/ 6/25 | Dyspnea, 1 year, visual disturbances, 5 months | 2 | 3 | 2-3 | | | 240 | 170 | 205 | 160 | 1 | 3 | 3 | 2/27/26 | 8 | |
| 11 | 40 Q | 10/ 1/24 | Hypertension, 4 years, visual disturbances, slight edema, loss of weight, 10 months, dyspnea, 4 months | 1 | 1 | 1 | | | 250 | 160 | 190 | 120 | 3 | 3 | 3 | March, 1925 | 6 | |
| 12 | 52 Q | 5/15/25 | Hypertension, 9 years, dyspnea on exertion and headache, visual disturbances, 1 year | 1 | 3 | 2-3 | | | 250 | 150 | 230 | 130 | 2 | 3 | 4 | 3/29/26 | 10 5 | |

| | | | | | | | | | | | | | | | | | | |
|----|----|---|---------------------|--|--------------|--------|--------|--------|-----|------------|------------|------------|------------|--------|--------|------------|------------|----------------|
| 13 | 39 | ♂ | 11/ 8/26 | Headache, 2½ years, hyper- tension and loss of weight, 2 years, visual distur- bances, 2 months | 70 1 | Normal | 1 | 2 | 220 | 110 | 160 | 120 | 3 | 2-3 | 1 | 4/ 3/27 | 5 | |
| 14 | 44 | ♂ | 9/23/25 | Headache, 2 years, visual disturbances, 1 year, dysp- nea, 2 months, attacks of diplopia | 75 0 | 2 | 1 | 3 | 1 | 240 | 160 | 225 | 125 | 3 | 2 | 2-3 | Jan , 1926 | 4 |
| 15 | 40 | ♀ | 9/ 3/25 | Headache, 1 year, loss of weight, 3 months, slight dyspnea | 47 2 | Normal | 1 | 2 | 1 | 260 | 170 | 190 | 120 | 2 | 3-4 | 2 | 2/10/26 | 5 |
| 16 | 37 | ♀ | 8/19/25 | Headache, dyspnea, precor- dial pain, and loss of weight, 1 year, visual dis- turbances and apoplectic stroke, 2 weeks | 81 3 | 3 | | 1+ | | 240 | 155 | 208 | 120 | 2 | 2 | 3 | 3/22/26 | 7 |
| 17 | 30 | ♀ | 7/29/26 | Hypertension and headache, 4½ years, loss of strength 1 year | 46 3 | Normal | 3 | 3 | | 245 | 165 | 185 | 140 | 1 | 2 | 1 | 10/22/26 | 3 |
| 18 | 24 | ♀ | 4/27/22 | Tuberculous infection of right ankle, 12 years, hypertension, 7 years, headache and visual dis- turbances, 2 months | 58 2 | Normal | 2 | 2 | | 280 | 190 | 210 | 140 | 2 | 2-3 | 2-3 | 3/23/23 | 11 |
| 19 | 45 | ♂ | 7/11/23 11/ 7/23 | Hypertension and headache, 2 years, loss of weight, 1 year | 75 0 66 8 | 1 1 | 1 1 | 2 2 | | 195 190 | 180 125 | 175 210 | 120 150 | 1 2 | 1 2 | 2-3 2-3 | 2/ 8/24 | 7 |
| 20 | 35 | ♂ | 7/27/25 | Headache and asthenia, 1 year | 64 5 | Normal | 2 | 3 | | 240 | 150 | 208 | 140 | 2 | 2 | | 3/ 6/26 | 7 |
| 21 | 40 | ♂ | 7/23/26 | Albuminuria, 7 years, at- tack of hematuria, 3½ years ago, hypertension and headaches, 1 year | 82 7 | 2 | 2 | 1 | | 210 | 120 | 210 | 150 | 1 | 2 | 2 | 8/ 8/27 | 12 5 |
| 22 | 50 | ♂ | 6/ 4/25 | Dyspnea, asthenia, slight visual disturbances, head- aches, dependent edema, 6 months | 86 4 | 2 | 1 | 3 | | 220 | 150 | 170 | 120 | 1 | 2 | 2 | 9/ 2/25 | 3 |
| 23 | 50 | ♀ | 4/19/26 | Headaches, asthenia, dysp- nea, 5 months, distur- bance of vision, 2 weeks, metrorrhagia | 60 0 | 1 | 1 | 2+ | | 240 | 160 | 180 | 115 | 2 | 2 | 3 | 8/ 6/26 | 3 5 |
| 24 | 45 | ♀ | 1/30/26 | Headache and vertigo, 2½ years, pain in back and loss of weight, 1 year | 60 0 | 1 | 1 | 1+ | 1 | 250 | 130 | 210 | 100 | 1 | 2 | 2 | Feb, 1927 | 12 |
| 25 | 45 | ♂ | 3/12/23 | Headache, 2 years, loss of weight, 3 months, hyper- tension, 5 weeks | 96 8 | 1 | 1 | 1 | | 225 | 145 | 175 | 95 | 2 | 2 | 4 | 5/ 9/26 | 38 |
| 26 | 46 | ♂ | 12/16/24 | Hypertension, 3 years, dysp- nea and edema, 7 months, visual disturbances, 4 months | | 2-3 | | 2 | 2 | 220 | 145 | 240 | 155 | 2 | 2-3 | 2 | 12/20/24 | 4† |
| | | | | | | | | | | | | | | | | | | Died, "stroke" |
| | | | | | | | | | | | | | | | | | | Neecropsy |

* In this table and in table 4, ♂ indicates male, ♀, female

† Days

TABLE 1—*Clinical Data on Admission—Continued*

| Case No. | Age and Sex | Date of Admission | History of Present Illness | Weight in lb. | Size of Aorta Grade | Second Aortic Sound, Pericardial | Blood Pressure | | | | | | Retinal Changes | | | Date of Death | Duration of Life from First Admission, Months | Comment |
|----------|-------------|---------------------|--|---------------|---------------------|----------------------------------|----------------|------------|------------|------------|------------|------------|-----------------|------------|-------------------------|---------------|---|--------------------------------|
| | | | | | | | Admission | Diastolic | Systolic | Diastolic | Systolic | Diastolic | Ratinitis | Scleritis | Arteriosclerosis, Grade | | | |
| 27 | 42 ♂ | 12/11/25 | History of Present Illness Pain in head and hypertension 4 years, dyspnea on exertion, 6 months, falling vision and loss of weight, 2 months | 65 1 | 1 | 3 | 1 | 210 | 110 | 180 | 100 | 2 | 2 | | | 3/ 3/26 | 2 | |
| 28 | 31 ♀ | 3/ 8/21 | Periodic attacks of asthenia, 4 years, marked hypertension and blindness of left eye, 4 months | 15 1 | Normal | 3 | 1-2 | 1 | 270 | 110 | 200 | 140 | 2 | 3 | 3-4 | 8/30/24 | 0 | |
| 29 | 40 ♂ | 11/ 3/23 | Headache and hypertension, 2 years, dyspnea, 4 months | 100 4 | 1 | 1 | 2 | 260 | 160 | 210 | 150 | 2 | 3 | | 1-2 | 7/ 1/24 | 8 | |
| 30 | 33 ♂ | 11/10/24 | Loss of memory, 3 years ago for 1 month, headache with vomiting for 8 months, visual disturbances, 2 weeks | 83 2 | 2 | 1 | 1 | 230 | 120 | 180 | 90 | 2 | 2 | 2 | 2 | 3/ 9/26 | 16 | Bilateral lumbar sympathectomy |
| 31 | 38 ♂ | 7/13/23 | Headache and loss of weight and strength, and dyspnea for 1 year, hypertension, 4 months | 66 0 | 2 | 3 | 2-3 | 235 | 155 | 230 | 140 | 2 | 3 | 1 | | 10/15/23 | 3 | |
| 32 | 36 ♂ | 8/18/23 | Headache, dyspnea and moderate edema, 3 years, attacks of unconsciousness, 2 1/2 years ago | 124 0 | 3 | 3 | 4 | 235 | 135 | 220 | 130 | 1-2 | 1-2 | 2 | 2 | 1/14/27 | 5 | Necropsy |
| 33 | 49 ♂ | 9/25/23 | Severe headache and hypertension, 2 years, hemiplegia 2 years ago, slight dyspnea and edema, 2 months | 63 2 | 2 | 1 | 3 | 215 | 140 | 210 | 150 | 1 | 2 | 1 | | 10/27/23 | 1 | |
| 34 | 39 ♀ | 7/12/23 | Hypertension and falling vision, 2 years, severe headache, 6 months, numbness of left hand, 3 to 4 months, dyspnea 1 year, dyspnea, 8 months, edema, 3 weeks | 110 0 | 2-3 | 2 | 1 | 200 | 185 | 240 | 110 | 3 | 2 | 3 | | 8/29/23 | 1 1/2 | |
| 35 | 42 ♂ | 7/20/25 11/23/25 | Headache and epistaxis, 1 year, dyspnea, 8 months, edema, 3 weeks | 68 2 | 2 2-3 | | 1 2 | 210 210 | 155 160 | 180 180 | 150 140 | 1-2 1-2 | 2 2 | 1-2 1-2 | | 2/18/26 | 7 | |
| 36 | 39 ♂ | 11/ 5/25 1/ 8/26 | Vertigo and double vision 2 years ago, hypertension, 15 months, slight dyspnea and falling vision, 1 week | 59 0 | 1 | 1 | 3 | 230 215 | 150 160 | 200 210 | 130 140 | 2 2 | 1-2 3 | 2 3 | | 5/10/26 | 6 | |

| St | Age | 8/23/21 | Visual disturbances, vertigo, weakness, dyspnea, 8 months, hemiplegia, hypertension, loss of weight (34 Kg.), 6 months | 65.0 | 1 | 1 | 1 | 2 | 1 | 250 | 140 | . | 2-3 | 3 | 2 | 8/31/21 | St | Necropsy | |
|----|------|----------|---|------|--------|---|-----|-----|-----|-----|-----|-----|-----|-----|-----|--------------|---------|---------------------------------------|--|
| 37 | 45 ♀ | 8/23/21 | Visual disturbances, vertigo, weakness, dyspnea, 8 months, hemiplegia, hypertension, loss of weight (34 Kg.), 6 months | 65.0 | 1 | 1 | 1 | 2 | 1 | 250 | 140 | . | 2-3 | 3 | 2 | 8/31/21 | 5† | | |
| 38 | 15 ♀ | 5/ 6/23 | Headache, 4 years, albuminuria, 2 years, left facial paralysis, 2 months | 53.6 | Normal | 2 | 2 | 2 | 2 | 200 | 140 | 170 | 115 | 2 | 2-3 | 1 | 4/ 4/27 | 11 | |
| 39 | 42 ♀ | 3/27/26 | Headache and vomiting, visual disturbances, right eye, hypertension, dyspnea, 6 months | 41.4 | 1 | 3 | 3 | 3 | 280 | 150 | 225 | 120 | 3-4 | 2 | 2 | 4/26/26 | 1 | Stroke of apoplexy while in hospital | |
| 40 | 19 ♀ | 2/20/26 | Headache, hypertension and periodic blurring of vision, 2 years, dyspnea and nervousness, 1 year, albuminuria, 8 months | 42.3 | 1 | 3 | 2 | 2 | 270 | 150 | 220 | 150 | 2 | 3 | 2 | 4/ 7/23 | 15 | Loss of weight | |
| 41 | 36 ♀ | 12/ 6/24 | Headache, 6 years, severe headache, dyspnea and cardiac pain, 3 months | 53.6 | 1 | 1 | 2+ | 2+ | 225 | 135 | 270 | 125 | 2 | 2 | 2 | 10/19/25 | 11 | | |
| 42 | 40 ♀ | 7/ 6/25 | Failing vision, 15 months; left hemiplegia and hypertension, 8 months | 63.6 | 4 | 3 | 1 | 1 | 204 | 140 | 220 | 160 | 2 | 3 | 2 | 7/31/26 | 25† | | |
| 43 | 35 ♂ | 1/27/25 | Hypertension, 6 years, visual disturbances and albuminuria, 10 months, pulmonary edema, 1 month ago | 84.1 | 3 | 2 | 2 | 2 | 240 | 165 | 220 | 120 | 3 | 3 | 3 | Summer, 1925 | 6 | | |
| 44 | 39 ♂ | 8/17/26 | Headache, 2 years; vertigo, dyspnea, visual disturbances left eye, 1 year, hypertension, numbness of left side 10 months | 63.2 | 1-2 | 2 | 3 | 3 | 240 | 155 | 210 | 140 | 3-4 | 2-3 | 2-3 | | | Necropsy, examination of kidneys only | |
| 45 | 45 ♂ | 7/21/25 | Headache, hypertension and nervousness 3 years, dyspnea and edema of ankles, 3 to 4 months | 74.1 | 1 | 1 | 2 | 2 | 220 | 150 | 165 | 110 | 1 | 3 | 3 | 3/ 9/25 | 8 | | |
| 46 | 28 ♂ | 5/14/25 | Dyspnea, tachycardia and trace of edema, 1 month | 86.4 | 3 | 3 | 2- | 2- | 220 | 160 | 175 | 120 | 2 | 2 | 2 | 1/22/26 | 8 | | |
| 47 | 53 ♂ | 3/14/25 | Insomnia and dyspnea, 2½ years, right hemiplegia, headache, vertigo, hypertension, edema of ankles, 18 months, loss of weight | 84.1 | 1-2 | 3 | 2-3 | 2-3 | 220 | 140 | 220 | 140 | 2-3 | 3 | 3 | 4/ 2/25 | 12.5 | Pulmonary edema in hospital | |
| 48 | 64 ♀ | 2/ 3/25 | Headache, vertigo, right hemiplegia, dyspnea, edema of legs 1 year, visual disturbances, 6 months | 60.5 | 2 | 2 | 2 | 2 | 220 | 190 | 180 | 100 | 2 | 3-4 | 4 | | | Hematuria in hospital | |
| 49 | 23 ♂ | 6/ 3/24 | Hypertension, 5 years, albuminuria, cylindruria, 3 months, headache, constant, 3 weeks | 66.8 | 1-2 | 2 | 3 | 3 | 245 | 145 | 220 | 120 | 2 | 2 | 3 | 7/19/24 | 1.5 | | |
| 50 | 54 ♀ | 6/ 2/25 | Hypertension, headache and vertigo, 3 years, attack of unconsciousness 6 months ago | 53.6 | 1 | 1 | 2 | 2 | 240 | 140 | 220 | 120 | 2 | 3 | 2 | 11/16/25 | 5.5 | | |

TABLE 1—Clinical Data on Admission—Continued

| Case No. | Age and Sex | Date of Admission | History of Present Illness | Weight, lb. | Heart, Grade | Aortic Sound | Size of Heart, Grade | Pericardial Effusion, Grade | Blood Pressure | | | | | | Retinal (Lenses) | | | Date of Death | Duration of Life from First Admission, Months | Comment |
|----------|-------------|--------------------|--|--------------|--------------|--------------|----------------------|-----------------------------|----------------|------------|------------|------------|--------|-----------|-------------------|-----------|--------------------|---------------|---|---------|
| | | | | | | | | | Sys | Diastolic | Sys | Diastolic | Sys | Diastolic | Arterio-sclerosis | Retinitis | Grade | | | |
| 51 | 31 ♀ | 6/10/25 | Headache and asthma, 8 months; dyspnea and edema of ankles, 5 months | 53.8 | 1 | 3 | 2 | 1 | 210 | 160 | 210 | 150 | 1 | 3 | 3 | 3 | Sept., 1925 | 3 | | |
| 52 | 45 ♂ | 7/15/26 | Headache, 7 years; hypertension, 1 year, loss of weight and dyspnea, 6 to 8 months | 72.3 | 1 | 2 | 2 | | 210 | 180 | 220 | 160 | 2 | 2 | 3 | 3 | 12/ 5/26 | 15 | | |
| 53 | 50 ♂ | 3/ 9/22 5/10/26 | Hypertension, 4 years, no subjective complaint, memory failure, 2 to 3 years; dyspnea with two attacks of pulmonary edema in last 6 months | 63.1 61.1 | 1 1 | 2 1 | 2 1 | | 190 210 | 110 160 | 170 235 | 115 155 | 1 2 | 1 2 | 3 3 | 3 | 6/21/26 | 51 | | |
| 54 | 59 ♂ | 12/ 2/21 | Dyspnea on exertion, 5 years; hypertension, headache, vertigo with vomiting and visual disturbances, 4 years | 101.1 | 2-1 | 1 | 2+ | 2 | 230 | 135 | 180 | 100 | 1 | 2 | 3 | 3 | 11/20/25 | 12 | Orthopnea and attack of pulmonary edema in hospital | |
| 55 | 13 ♀ | 1/ 8/25 | Headache and hypertension, 7 years; dyspnea and edema of feet, 4 years; orthopnea and dependent edema, 5 months | 92.3 | 2 | 2 | 2 | 1-2 | 280 | 150 | 220 | 125 | 2 | 3 | 2 | | | | | |
| 56 | 15 ♂ | 7/26/25 1/25/26 | Persistent dyspnea and dependent edema; subconjunctival hemorrhage, diplopia, blurred vision, 2 months; headache, 2 weeks | 89.5 55.0 | 2 Normal | 2 3 | 2 3 | 2 | 215 160 | 100 100 | 260 110 | 180 110 | 2 1 | 3 1 | 2 2 | 2 | 9/ 6/25 3/20/26 | 5 2 | | |
| 57 | 18 ♀ | 12/18/21 | Metrorrhagia, 4 years; dyspnea and edema of ankles, 1 year | 87.3 | 1 | 1 | 1 | 1 | 205 | 125 | 170 | 95 | 1 | 2 | 3 | 3 | 1/ 6/27 | 21.5 | "Stroke," Sept., 1923 | |
| 58 | 34 ♂ | 1/ 2/26 | Headache, weakness and loss of weight, 2 years; attack of unconsciousness 5 months ago | 70.0 | 1 | 2 | 2 | 1 | 215 | 160 | 195 | 110 | 2 | 3 | 2 | 2 | 3/23/27 | 15 | Essential hematuria, cystoscopic examination | |
| 59 | 27 ♀ | 9/25/21 | Intermittent attacks of hematuria, 6 years; hypertension and headache, 10 months | 58.0 | 1 | 3 | 1— | | 250 | 110 | 220 | 135 | 2 | 3 | 2 | | | | | |

[illegible]

TABLE 1—Clinical Data on Admission—Continued

| Case No. | Age and Sex | Date of Admission | History of Present Illness | Weight, kg | Heart, ton, Grade | Second Aortic Sound | Pulmonary | Blood Pressure | | | | Retinal Changes | | Date of Death | Duration of Life From First Admission, Months | Comment | | |
|----------|-------------|-------------------|--|------------|-------------------|---------------------|-----------|----------------|-----------|-----------|--------------------------|-----------------|---|---------------|---|----------|----|---|
| | | | | | | | | Admission | Dismissal | Retinitis | Arterio-sclerosis, Grade | | | | | | | |
| 71 | 51 ♀ | 1/2/25 | Hypertension and dyspnea, 6 years, weakness, dimness of vision, loss of weight, 1 year | 70.0 | 2 | 1 | 1-2 | 1— | 270 | 160 | 210 | 170 | 3 | 2-3 | 2 | 8/7/25 | 7 | |
| 72 | 40 ♀ | 7/10/25 | Miscarriage, 16 months ago, since then headache, weakness and loss of weight | 64.5 | 1 | 3 | 1— | 1— | 250 | 180 | 210 | 165 | 2 | 3 | 2 | 9/1/25 | 2 | Right hemiplegia in hospital |
| 73 | 31 ♂ | 4/18/21 | Headache, 2 to 3 years, dimness of vision, 6 months, epileptiform convulsions 6 weeks ago | 56.8 | Normal | 1 | 1 | | 200 | 160 | 225 | 155 | 3 | 3 | 3 | 7/8/21 | 25 | Question of tumor cerebri |
| 74 | 43 ♂ | 9/19/24 | Hypertension and headache, 3½ years, dyspnea, 6 months, blurred vision, 1 month | 61.0 | 1 | 2 | | | 250 | 160 | 220 | 130 | 2 | 2-3 | 3 | 2/23/25 | 55 | |
| 75 | 54 ♂ | 7/22/21 | Attack of frontal headaches, vertigo, vomiting, right hemianopia 8 months ago, vertigo and aphasia since | 85.0 | Normal | 3 | 3 | | 215 | 130 | 160 | 100 | 2 | 3 | 3 | 10/31/21 | 3 | |
| 76 | 48 ♂ | 8/13/26 | Periodic severe headache, 3 years, convulsions, blurred vision, albuminuria, 6 months | 52.3 | Normal | 1 | 1-2 | | 240 | 180 | 220 | 140 | 3 | 3 | 4 | | | Question of tumor cerebri |
| 77 | 45 ♂ | 11/1/23 | Hypertension and albuminuria, 5 years, headache, 1 year, insomnia and loss of weight, 7 months | 75.9 | 2 | 2 | 2 | | 250 | 190 | 190 | 145 | 3 | 2-3 | 2-3 | 12/25/23 | 2 | |
| 78 | 30 ♂ | 2/6/23 | Headache, 3 years, severe headache, hypertension and loss of weight, 1 year | 64.1 | 1 | 1 | 2 | | 250 | 175 | 195 | 115 | 4 | 3 | 3 | 7/28/23 | 6 | Lost 15 pounds in last year |
| 79 | 40 ♂ | 12/21/20 | Nocturia, 1 year, falling vision, 7 months | 50.4 | 1 | | 2-3 | | 240 | 160 | 225 | 140 | 4 | 3 | | 1/29/21 | 1 | Convulsion in hospital, question of tumor cerebri |
| 80 | 62 ♂ | 8/11/25 | Headaches for 6 years, hypertension, loss of memory, dyspnea, asthenia, falling vision, 7 months, loss of weight | | 2 | | 3 | | 240 | 120 | 200 | 100 | 2 | 3 | 3 | 8/19/25 | 8† | Necropsy |
| 81 | 50 ♂ | 1/27/27 | Dyspnea, 1 year, marked dyspnea, 4 months, general convulsions in hospital | 95.5 | 3 | 1 | 2 | 3 | 220 | 140 | 225 | 130 | 2 | 1-2 | 2 | 3/7/27 | 1 | Necropsy |

At the time of examination, only one case did not show distinctly high blood pressure. The patient was asthenic. The systolic blood pressure on admission was 160 and the diastolic, 100. After a stay in the hospital the patient gained in weight and the blood pressure rose to 190 systolic and 110 diastolic. In eighty cases the maximal systolic reading varied from 220 to 280 and the diastolic from 120 to 190.

With one exception, retinitis was present in all cases at every examination. In one case, a typical but mild retinitis observed at the first examination completely subsided while the patient was under observation. In the series the retinitis varied in grade from mild, with only slight papilledema and a few exudates and areas of hemorrhage, to severe, with as much as 6 diopters swelling of the optic disk, extensive edema of the retina, and many areas of hemorrhage and exudates of various types. In more than half of the cases, the retinitis was of moderate severity with papilledema of less than 2 diopters. In ten cases, the swelling of the disks measured 3 or more diopters. While forty-three of the patients complained of blurred vision, central vision was definitely reduced objectively in only half that number. The impairment of vision seems to be associated with the spread of the edema into the macular region in the second stage of the retinitis. In three cases, there was a definite unilateral central scotoma associated with edema in the macular region. With recession of the edema and the appearance of a partial macular star, the scotoma disappeared. In one case right homonymous hemianopia, apparently due to a cerebral vascular accident but not associated with hemiplegia, was present. In one case, vision in one eye was reduced to perception of light by extensive hemorrhage into the vitreous. In most cases the vision was surprisingly good. Detailed data are incorporated in table 1.

LABORATORY TESTS

Certain laboratory tests were usually carried out as a routine. The results are detailed in table 2. The absence of anemia suspected from the examination of the mucous membranes was confirmed in sixty-six cases. If anemia was present, there was usually a history of bleeding. Epistaxis occurred in two cases, petechiae in two, uterine bleeding in two, hematuria in five and in two cases, profuse bleeding followed tonsillectomy. In one case in which anemia was present, therapeutic phlebotomy had recently been performed twice. Hemoglobin was determined by the Dare, carbon monoxide and acid-hematin⁵ methods. Thus, the absence of clinical signs of anemia and negative laboratory evidence

⁵ Osgoode, E. E., and Haskins, H. D. A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, *J Biol Chem* **57** 107, 1923. Palmer, W. W. The Colorimetric Determination of Hemoglobin, *J Biol Chem* **33** 119, 1918.

TABLE 2.—Laboratory Data on Admission

| Case | Blood* | | | | | | | | | | Urine | | | Phenol sulphonaphthalic per Cent | | | Chloride Test, Percentage | | Output After Water, Ind. cc |
|---|------------|------------------------|------------------------|-------------------|-------------------------|------------------------|-----------|-----------------------|-----------------|------|------------------|--------------|---------|----------------------------------|--------|-------|---------------------------|--|-----------------------------|
| | Hemoglobin | | | | | Creatinine | | | | | Specific Gravity | Albumin | Castles | Cent | Before | After | | | |
| | 1 rth | Hemo- globin, per Cent | Hemo- globin, per Cent | Urea, Mr per Cent | Crat- Acid, Mr per Cent | Uric Acid, Mr per Cent | Viscosity | With Coagulation Test | With Water Test | | | | | | | | | | |
| 1 Normal | 111 | 514 | 85 | 28 | 18 | 24 | 1005 | 1070 | 1070 | 1005 | 0-1 | Rare hyaline | 60 | | | | 1,350 | | |
| 2 Normal | 117 | 140 | 75 | 112 | 28 0 | 13 | 1005 | 1020 | 1020 | 1000 | 0-1 | | 40 | | | | 1,315 | | |
| 3 Normal, second admission | 160 | 160 | 70 | 32 | 18 | 32 | 1001 | 1031 | 1028 | 1001 | 0 1 | 0 1 | 55 | | | | 1,005 | | |
| 4 Normal | 111 | 160 | 83 | 36 | 18 | 31 | 1001 | 1027 | 1027 | 1001 | 1-3 | 1 3 | 60 | | | | 1,115 | | |
| 5 Inverted T wave in I | 160 | 160 | 70 | 29 | 16 | 31 | 1002 | 1021 | 1021 | 1002 | 0-2 | Hyaline 1 2 | 60 | | | | | | |
| 6 Premature contractions | 130 | 112 | 72 | 13 28 | 11 16 | 2 8 3 0 | 1006 | 1031 | 1031 | 1004 | 1 | Occasional | 65 | | | | 1,625 | | |
| 7 Inverted T wave in I | 170 | 78 | 100 | 27 | 14 | 36 | 1000 | 1024 | 1024 | 1000 | 0-1 | | 50 | | | | | | |
| 8 Inverted T wave in all leads | 420 | 70 | 68 | 18-37 | 13 | 40 | 1010 | 1013 | 1020 | 1002 | 0-2 | Rare hyaline | 35 | | | | | | |
| 9 Inverted T wave in all leads | 360 | 70 | 111 | 17-18 | 20 | 48 5 1 | 1002 | 1020 | 1020 | 1000 | 0-1 | Occasional | 50 | | | | 880 | | |
| 10 Inverted T wave in I and II | 420 | 70 | 137 | 30-35 | 17 | 4 8 5 1 | 1006 | 1013 | 1013 | 1000 | 1 | | 53 | | | | | | |
| 11 Inverted T wave in I and II | 420 | 72 | 154 | 20-20 | 15 | 3 2 | 1016 | 1021 | 1021 | 1000 | 0-2 | Occasional | 50 | | | | 1,550 | | |
| 12 Normal | 420 | 78 | 15 | 15 | 18 | | 1000 | 1020 | 1020 | 1000 | 1 | | 55 | | | | | | |
| 13 Inverted T wave in I and II | 377 | 74 | 115 | 21-31 | 10 | | 1005 | 1016 | 1020 | 1005 | 1-2 | Occasional | 20 30 | | | | | | |
| 14 Normal | 410 | 71 | 122 | 39 | 15 | | 1005 | 1020 | 1020 | 1005 | 1-2 | Occasional | 35-40 | | | | | | |
| 15 Inverted T wave in all leads | 430 | 70 | 115 | 22 | 13 | | 1010 | 1025 | 1025 | 1000 | 0-1 | Rare | 70 | | | | | | |
| 16 Inverted T wave in I, slurred Q R S in I | 496 | 78 | 118 | 17-10 | 18 | | 1009 | 1022 | 1022 | 1002 | 0-2 | Rare | 50 75 | | | | | | |
| 17 Normal | 460 | 70 | 155 | 18 | | | 1009 | 1021 | 1021 | 1002 | 1-3 | | 45 | | | | | | |
| 18 Normal | 460 | 75 | 122 | 24-35 | 16-17 | 30 | 1018 | 1018 | 1018 | 1000 | 1-3 | 1 | 35 | | | | 1,325-1,405 | | |
| 19 Normal | 436 | 70 | 86 | 17 32 | 18-21 | | 1000 | 1019 | 1019 | 1000 | 0-2 | 1 | 40 | | | | 26 | | |
| 20 Normal | 510 | 75 | 146 | 36-50 | 18 | 38 | 1006 | 1025 | 1025 | 1000 | 1-3 | 1 | 55 | | | | | | |
| 21 Inverted T wave in I | 350 | 58 | 58 | 28-42 | 11 | | 1002 | 1025 | 1025 | 1002 | 0-1 | | 40-45 | | | | 1,115 | | |
| 22 Inverted T wave in I and II | 400 | 70 | 29 31 | 22 31 | 18 | | 1002 | 1026 | 1018 | 1002 | 0-1 | Rare | 40 | | | | 1,600 | | |
| 23 Normal | 470 | 78 | 110 | 22 32 | 17 | 37 | 1002 | 1027 | 1027 | 1002 | 0-1 | 1 | 65 | 0 8 | 1 1 | | 1,110 | | |
| 24 Q R S notched | 420 | 78 | 99 | 115 36-41 | 1 | 46 | 1015 | 1020 | 1020 | 1002 | 1-2 | 1 | 20 | | | | | | |
| 25 Inverted T wave in I and II | 117 | 63 | 142 | 46-62 | 17 22 | | 1001 | 1022 | 1022 | 1001 | 1-2 | 1 | 40 | | | | | | |
| 26 Normal | 160 | 75 | 155 | 18-26 | 18 | 17 | 1005 | 1023 | 1023 | 1001 | 0-2 | Rare | 60-80 | | | | 1 0 | | |
| 27 Normal | 111 | 160 | 178 | 37 | 23 | 51 | 1003 | 1026 | 1026 | 1003 | 1-2 | 1-3 | 40 | 0 6 | 1 3 | | 3 2 | | |
| 28 Normal | 423 | 73 | 170 | 16-20 | 16 | 40 | 1005 | 1030 | 1030 | 1005 | 0-1 | Occasional | 50-70 | 0 7 | 1 2 | | 1,355 | | |
| 29 Normal | 423 | 73 | 170 | 16-20 | 16 | 40 | 1005 | 1030 | 1030 | 1005 | 0-1 | Occasional | 40 | | | | | | |
| 30 Inverted T wave in I and II | 15 | 81 | 168 | 52-83 | 33 5 3 | | 1001 | 1019 | 1019 | 1001 | 0-2 | 1 | 10 20 | | | | | | |
| 31 Inverted T wave in I and II | 544 | 81 | 168 | 29 | 23 | 3 6 | 1004 | 1019 | 1019 | 1001 | 0-2 | 1 | 55 | | | | 55 | | |
| 32 Inverted T wave in I and II | 170 | 72 | 165 | 47 66 | 22-32 | | 1005 | 1025 | 1025 | 1005 | 1-2 | 1 | 25 | | | | 25 | | |
| 33 Inverted T wave in II and III | 170 | 72 | 165 | 47 66 | 22-32 | | 1003 | 1013 | 1012 | 1003 | 1-2 | | | | | | | | |
| 34 Normal | 522 | 84 | 193 | 15 | 13 | 42 | 1010 | 1021 | 1021 | 1001 | 0-2 | 1 | 50 | | | | | | |
| 35 Normal | 383 | 70 | 138 | 30-34 | 17 | | 1010 | 1020 | 1020 | 1001 | 1 | 2 | 40 | | | | | | |
| 36 Normal | 130 | 75 | 155 | 18 | | | 1009 | 1021 | 1021 | 1002 | 1-3 | | 45 | | | | | | |

| | | | | | | | | | | | |
|----|---|-----|----|--------|-------|-----------|------|------|------------|-------|---------|
| 37 | Normal | 510 | 82 | 34 | 10 | 1006-1026 | 1006 | 1 | Occasional | 55-70 | 905 |
| 38 | | 163 | 80 | 27 | | 1000-1026 | 1001 | 1-2 | | 35 | 1,270 |
| 39 | | 112 | 76 | 18 | | 1011-1015 | | 1-2 | | 45 | |
| 40 | Normal | 101 | 75 | 23-32 | 16 | 1006-1027 | 1006 | 1-3 | 1 | | |
| 41 | | +11 | | | | | | | | | |
| 42 | | +20 | | | | | | | | | |
| 43 | | +13 | | | | | | | | | |
| 44 | | +5 | | | | | | | | | |
| 45 | | +5 | | | | | | | | | |
| 46 | Notched Q R S in I and III | 150 | 73 | 10-24 | 11 | 1000-1025 | 1000 | 1 | Rare | 40-55 | 1,075 |
| 47 | Inverted T wave and slurred Q R S in I and II | 186 | 82 | 29 | 20 | 1006-1016 | 1006 | 1 | | 40 | |
| 48 | | 120 | 79 | 27 | 16 | 1006-1016 | 1006 | 1 | | 40 | 540 |
| 49 | | +20 | | | | | | | | | |
| 50 | Inverted T wave in I and II | 504 | 76 | 19-35 | 15-17 | 1001-1020 | 1001 | 1 | | 60 | 620 |
| 51 | Normal | 380 | 75 | 32-36 | 18 | 1001-1015 | 1001 | 1 | | 55 | 1,180 |
| 52 | Inverted T wave in I and II | 172 | 82 | 30-36 | | 1005-1026 | 1005 | 1-2 | Occasional | | |
| 53 | Inverted T wave in all leads | 120 | 73 | 33-40 | 20 | 1001-1023 | 1001 | 1-2 | Rare | 30 | 975 |
| 54 | Inverted T wave in I | 150 | 73 | 23 | 17 | 1001-1020 | 1001 | Tr | | 45 | 1,770 |
| 55 | Inverted T wave in all leads | 170 | 71 | 10-36 | 15 | 1001-1020 | 1001 | 1-2 | 1 | 60 | 305 565 |
| 56 | | +22 | | | | | | | | | |
| 57 | | +28 | | | | | | | | | |
| 58 | Inverted T wave in II and III | 130 | 73 | 22 | 12 | 1001-1020 | 1001 | Tr | | 40 | 760 |
| 59 | Inverted T wave in I | 132 | 70 | 25-33 | 18-20 | 1003-1025 | 1003 | Tr | Rare | 45 | |
| 60 | Inverted T wave in all leads | 180 | 75 | 38-39 | | 1000-1018 | 1000 | 1-2 | 1 | 35 45 | 1,360 |
| 61 | | +6 | | | | 1003-1030 | 1003 | 1 | Rare | 45 55 | 710 |
| 62 | Normal | 150 | 76 | 17-53 | 19-21 | 1014-1025 | 1003 | 1-2 | Occasional | 50 | |
| 63 | Inverted T wave in I | 100 | 70 | 21-35 | 16 | 1010-1030 | | 1-2 | Rare | 40 | |
| 64 | Inverted T wave in all leads | 172 | 77 | 70-102 | 23-50 | 1001-1016 | 1001 | 1-2 | Rare | 25-30 | 525 |
| 65 | Inverted T wave in I | 452 | 65 | 15-36 | 13 | 1010-1025 | | 1-2 | | 50 | |
| 66 | Inverted T wave in I and II | 130 | 73 | 23-26 | 13 | 1002-1021 | 1002 | 1-2 | Rare | 45 | 1,275 |
| 67 | Inverted T wave in I and II | 133 | 75 | 18-34 | 15 | 1000-1020 | 1000 | 1 | | 50 35 | 1,275 |
| 68 | | 472 | 80 | 18-19 | 17 | | | Tr | | 50 | |
| 69 | Inverted T wave in I and II | 116 | 72 | 26-34 | 14-16 | 1002-1024 | 1002 | 1 | 1 | 45 | 1,375 |
| 70 | Inverted T wave in I and II | 520 | 77 | 32-48 | 23 | 1002-1018 | | 1-2 | | 45 | |
| 71 | Inverted T wave in I and II | 368 | 61 | 82-115 | 34-41 | 1005-1010 | | 1-2 | | 10 | |
| 72 | Inverted T wave in I and II | 118 | 77 | 16-19 | 11 | 1010-1023 | | 1 | | 80 | |
| 73 | Inverted T wave in I | 118 | 71 | 28-34 | 11 | 1003-1025 | 1003 | 1 | Occasional | 15 | 1,055 |
| 74 | | +7 | | | | 1009-1018 | | 1-2 | Rare | 40 | |
| 75 | Normal | 171 | 75 | 33 | 18 | | | 1-2 | | 45 | |
| 76 | Inverted T wave in I, slurred Q R S in I and II | 436 | 70 | 32-41 | 20 | 1013-1020 | | 1-2 | | | |
| 77 | | | | | | | | | | | |
| 78 | Inverted T wave in I | 420 | 80 | 18 | 19 | 1000-1025 | 1000 | 0-Tr | Rare | 60 | 1,325 |
| 79 | Inverted T wave in II and III | 110 | 76 | 22-24 | 16 | 1010-1029 | | 0-Tr | | 55 | |
| 80 | Inverted T wave in all leads | 378 | 67 | 28-53 | 24 | 1003-1012 | 1003 | 0-1 | | 25 | 1,115 |
| 81 | Inverted T wave in I | 352 | 70 | 11 | 15 | 1003-1016 | | 1 | | 40 | 900 |
| 82 | Inverted T wave in I | 120 | 72 | 23-134 | 21 | 1000-1016 | 1000 | 1-2 | 1 | 35-40 | 1,110 |
| 83 | | 116 | 74 | 35-46 | 15 | 1003-1030 | 1003 | 1-2 | 1-2 | 70 | 1,030 |
| 84 | Inverted T wave in all leads | 460 | 72 | 22-38 | 16 | 1002-1023 | 1002 | 1 | Occasional | 35-50 | 885 |
| 85 | Normal | 421 | 83 | 33-39 | 18-19 | 1000-1022 | 1000 | 1 | | 55 | 1,575 |
| 86 | | -7 | | | | 1001-1020 | 1000 | 0-2 | Rare | 50-75 | 759 |
| 87 | | +12 | | | | | | 1-2 | | 45 | 1,080 |
| 88 | | +10 | | | | 1001-1020 | 1001 | 1-2 | | | |
| 89 | | +32 | | | | | | | | | |
| 90 | Inverted T wave in I and II | 490 | 79 | 25-55 | 24-27 | 1009-1015 | | 1-2 | 1 | 35 | 0 1 |
| 91 | | 160 | 60 | 34-42 | 16 | 1004-1016 | | 1-3 | 1-3 | 40 | |
| 92 | Normal | 462 | 87 | 40-101 | 20-45 | 1012-1018 | | 1 | Occasional | | |
| 93 | Auricular premature contraction, inverted T wave and slurring of Q R S in all leads | 350 | 62 | 88-141 | 43-71 | 1006-1020 | | 1-2 | | | |

* The Wassermann reaction with the blood was negative in the seventy-five cases tested, except in case 64, in cases 7, 28, 58 and 79, the Wassermann reaction on the spinal fluid was negative
† Normal before infection, from 08 to 19, after infection, from 18 to 20
‡ Blood urine ailed, Fohn and Wu method (J Biol Chem 38 81, 1919)

were in striking contrast to what one usually sees in advanced cases of chronic glomerulonephritis. A definite history of the characteristic manifestations of syphilis was not obtained in any case. The Wassermann test was carried out in seventy-five of the eighty-one cases. In only one of these was it positive, although in a second case the patient's physician had reported a previous positive reaction and had instigated intensive treatment. Of the five cases in which the test was not carried out, in one, necropsy did not reveal distinct evidence of syphilitic involvement. The Wassermann test was also negative in the spinal fluid in four cases. Such evidence indicates that syphilis is not important etiologically in the malignant form of hypertension.

Electrocardiographic tracings were taken in seventy cases. Auricular fibrillation occurred in a single case and slurring of the Q R S waves was present in three cases. The only other abnormality encountered was inversion of the T wave. Significant inversion occurred in forty-four cases. In two cases the T waves became negative between the first and second admission. Thirty of these forty-four patients died within a year, confirming Willis' observation⁶ of the prognostic significance of inversion of the T wave (table 3). However, one must note that inversion of the T wave was not found in twenty cases in which death occurred within a period of one year. It is of interest that in ten cases in which the T wave was inverted in all three leads, obvious cardiac decompensation occurred in only three. The capillaries of the nail-fold were observed by G. E. Brown, according to the Lombard technic, in twenty-one cases. It soon became evident that abnormalities in the capillary blood flow occurred in many of these cases, and this was, in rare instances, accompanied by structural changes in the capillaries themselves, the most important of which was the definite tortuosity and contraction of the loops. The most notable change in blood flow was to the fast, intermittent or spurting type. This was noticeable in half of the cases (table 4).

The extent of the renal injury was estimated by (1) the presence or absence of albuminuria and, when present, the amount, (2) the presence or absence of cylindruria and when present, the grade, (3) the excretion of phenolsulphonphthalein, (4) the water output after the water test of Volhard and Fahr⁷ (5) the range of specific gravity

6 Willis, F. A. Observations of Negativity of the Final Ventricular T Wave on the Electrocardiogram, *Am J M Sc* 160 844, 1920, *Electrocardiograph and Prognosis. I. Significant T Wave Negativity in Isolated and Combined Derivations of the Electrocardiogram*, *Arch Int Med* 30 434 (Oct) 1922.

7 Volhard, Franz. Die doppelseitigen hämatogenen Nierenerkrankungen (Brightsche Krankheit), Berlin, Julius Springer, 1918. Volhard, Franz, and Fahr, K. T. Die Brightsche Nierenerkrankung, *Klinik, Pathologie und Atlas*, Berlin Julius Springer, 1914.

following the water test and concentration test of Volhard and Fahr, (6) the determination of the concentration of urea in the blood, (7) the estimation of the concentration of creatinine in the blood, (8) the estimation of the concentration of uric acid in the blood, (9) the chloride excretion during a control period and after intravenous injection of 10 per cent sodium chloride solution, (10) the sodium benzoate test of Kingsbury and Swanson⁸ and (11) the urea index, as advocated by Van Slyke⁹. The application of tests 9, 10 and 11 was limited to a few cases.

Albumin was graded from 0 to 3, cylindruria was often absent and was present up to grade 4. From the standpoint of excretory efficiency of the kidney, renal function was estimated on the basis of the output of phenolsulphonphthalein, the variation in the specific gravity of the urine, the amount of water excreted under given conditions and the concentration in the blood of urea, creatinine and uric acid. On the basis of the foregoing tests, our cases at the time of initial examination fall into four

TABLE 3—*Electrocardiograms with Alterations in the T Wave*

| | Cases |
|--|-------|
| T wave inverted in lead I | 14 |
| T wave inverted in leads I and II | 18 |
| T wave inverted in leads II and III | 2 |
| T wave inverted in leads I, II and III | 10 |

groups, normal and mild, moderate and severe renal insufficiency. In twenty-one cases renal function was comparatively normal, in forty-six, insufficiency was mild, in seven, it was moderate and in seven, it was severe. Of the cases in which it was severe, definite cardiac decompensation was present in three (table 5). In two cases there was decreased specific gravity, associated with a high output of water (1,575 to 1,770 cc), a condition of hyposthenuria. In four other cases, decreased specific gravity accompanied a good output. In two cases in which the concentration was low, the water output was markedly reduced (from 500 to 620 cc). In five cases, there was a similar decrease in specific gravity with moderately reduced output. In seven cases in which the sodium chloride test was carried out, six showed normal or slightly reduced concentration while one showed markedly diminished output. The sodium benzoate test was carried out in a single case, and a normal result was obtained. The urea index of Van Slyke⁹ was determined in

8 Kingsbury, F. B., and Swanson, W. W. The Synthesis and Elimination of Hippuric Acid in Nephritis. A New Renal Function Test, *Arch. Int. Med.* 28:220 (Aug.) 1921.

9 Van Slyke, D. D. Urea Index Formula, personal communication to the authors. Van Slyke, D. D., and Cullen, G. E. A Permanent Preparation of Urease and Its Use in the Determination of Urea, *J. Biol. Chem.* 19:211, 1914.

TABLE 4—*Studies on the Cardiovascular System*

| Capillaries of the Nail Folds | | | | | | | | | | | | | | | | |
|-------------------------------|-----|-----|-----------------------------|----------------------|-----------------------|------------------|--|---------------------|------------------------|------------------------|----------------------------|------|--------------|------|--|------------------------------------|
| Case No. | Sex | Age | Blood Pressure on Admission | Enlargement of Heart | Pericardial Sclerosis | Pulsation, Grade | Retinal Sclerosis by Ophthalmoscope, Grade | Morphologic Changes | | | Functional Changes in Flow | | | | Inter-rupted | Significant Changes in Capillaries |
| | | | | | | | | Tortuosity of Loops | Straight-ness of Loops | Con-formation of Loops | Uniform | | Intermittent | | | |
| | | | | | | | | | | | Fast | Slow | Fast | Slow | | |
| 1 | ♀ | 52 | 230 | 160 | 1 | 1 | 3* | + | +++ | +++ | ++ | ++ | ++ | ++ | Definite disturbance in flow, tortuosity and contraction excessive for age | |
| 3 | ♂ | 46 | 220 | 110 | 1 | 1-2 | 1 | + | ++ | ++ | ++ | ++ | ++ | ++ | Contraction marked for age, normal fast flow | |
| 5 | ♂ | 40 | 235 | 150 | 1 | 1-2 | 2 | ++ | ++ | ++ | ++ | ++ | ++ | ++ | Changes moderately marked for age, definite disturbance in flow, spastic type | |
| 6 | ♀ | 53 | 210 | 175 | 1 | 1 | 3-4* | + | +++ | +++ | ++ | ++ | ++ | ++ | Marked contraction for age, mild disturbance in flow | |
| 7 | ♀ | 25 | 210 | 165 | Normal | 1 | 1* | + | + | ++ | ++ | ++ | ++ | ++ | Very slight changes in form and flow | |
| 17 | ♀ | 30 | 245 | 165 | Normal | 3 | 1 | + | + | ++ | ++ | ++ | ++ | ++ | Normal appearance and flow | |
| 19 | ♀ | 24 | 280 | 190 | 1 | 2 | 2 | ++ | ++ | ++ | ++ | ++ | ++ | ++ | Mild changes in form, marked disturbance in flow | |
| 21 | ♀ | 24 | 250 | 190 | 1 | 1-2 | 3-4* | ++ | +++ | +++ | ++ | ++ | ++ | ++ | Contraction and tortuosity out of proportion to age | |
| 28 | ♀ | 31 | 270 | 110 | 1 | 1-2 | 3-4* | ++ | +++ | +++ | ++ | ++ | ++ | ++ | marked disturbance in flow | |
| 30 | ♂ | 33 | 230 | 120 | 2 | 1 | 2 | + | ++ | ++ | ++ | ++ | ++ | ++ | Mild contraction and mild disturbances in flow | |
| 31 | ♂ | 38 | 255 | 155 | 2 | 2-3 | 1 | + | +++ | +++ | ++ | ++ | ++ | ++ | Contraction excessive, decreased number of open capillaries | |
| 32 | ♂ | 30 | 210 | 130 | 2 | 2 | 1 | + | +++ | +++ | ++ | ++ | ++ | ++ | Changes in form excessive, retarded flow observed in evidence decompensation | |
| 38 | ♀ | 15 | 200 | 138 | Normal | 2 | 1-- | | + | + | | | | + | No changes in form, disturbance in flow limited to isolated capillaries | |
| 44 | ♀ | 39 | 240 | 155 | 1 | 3 | 2-3 | + | +++ | +++ | ++ | ++ | ++ | ++ | Contraction and disturbance in flow distinctly abnormal | |
| 50 | ♀ | 27 | 230 | 140 | 1 | 1-- | 2* | ++ | +++ | +++ | ++ | ++ | ++ | ++ | Excessive contraction and accelerated flow | |
| 60 | ♀ | 9 | 190 | 130 | Normal | 1 | 1-- | | ++ | ++ | ++ | ++ | ++ | ++ | Marked disturbance in flow | |
| 61 | ♀ | 48 | 210 | 140 | 1 | 2 | 2-3* | +++ | +++ | +++ | ++ | ++ | ++ | ++ | Changes in form marked, flow abnormal | |
| 71 | ♀ | 31 | 270 | 160 | 2 | 1-2 | 2* | | ++ | ++ | ++ | ++ | ++ | ++ | Flow probably abnormal | |
| 71 | ♀ | 43 | 250 | 160 | 1 | 2 | 3 | ++ | ++ | ++ | ++ | ++ | ++ | ++ | Marked lengthening and moderate contraction of loops, mild disturbance of flow | |
| 76 | ♂ | 18 | 240 | 180 | 1 | 1-2 | 4* | | +++ | +++ | | | | | A few loops showed marked contractions, definite disturbance in flow | |
| 77 | ♂ | 15 | 230 | 190 | 2 | 2 | 2-3* | | ++ | ++ | ++ | ++ | ++ | ++ | Contraction marked for age, accelerated flow | |
| 78 | ♂ | 39 | 250 | 175 | 1 | 2 | 3 | | +++ | +++ | ++ | ++ | ++ | ++ | Contraction marked for age with early disturbance in flow | |

* The grade of retinal sclerosis appeared more marked than the actual grade present because of perivascular gliosis

three cases, being within normal limits in two and moderately reduced in one. It is important to point out that in sixty cases the blood urea was 40 mg or less, in only sixteen cases was the blood creatinine abnormally high, ranging from 2.1 to 7.1 mg, and uric acid, when estimated, was never found above 5.1 mg for each hundred cubic centimeters of blood.

The basal metabolic rate was determined in thirty-nine of the cases in the present series. In fourteen the rate was normal, varying between -10 and $+10$, and the thyroid gland on palpation was normal. In seventeen cases the rate varied between $+10$ and $+20$, in three of these, small adenomas of the thyroid were present, but clinical symptoms of hyperthyroidism were not present. In eight cases the rate was between $+20$ and $+40$, and this increased rate was maintained in the five in which a second estimation was made. In this group of eight cases, adenomas of the thyroid were present in two, but clinical evidence of

TABLE 5—Renal Function at Time Retinitis Was First Observed

| | Cases Grouping Approximate | Phenol- sulphon- phthalein, per Cent | Specific Gravity, Range | Water Output, Cc | Blood Urea, Mg | Blood Creatinine, Mg |
|------------------------|----------------------------------|---|-------------------------------|------------------------|----------------------|----------------------------|
| Normal | 21 | 45 to 75 | 1.003 to 1.025 | 1,100 or more | Below 40 | Below 2.0 |
| Mild insufficiency | 46 (1)* | 35 to 40 | 1.003 to 1.020 | 900 to 1,000 | 35 to 40 | Below 2.0 |
| Moderate insufficiency | 7 (1)* | 20 to 35 | 1.003 to 1.020 | 600 to 800 | 40 to 70 | 1.7 to 3.2 |
| Severe insufficiency | 7 (3)* | Below 20 | Less than 1.003 to 1.020 | Less than 500 | 80 to 144 | 2.1 to 7.1 |

* Cases in which myocardial decompensation was present

hyperthyroidism could not be demonstrated. This moderately increased metabolism in eight cases was apparently not caused by a diseased thyroid. This increase in metabolism confirms the observations of Du Bois, Boas and Shapiro, and others.¹⁰

THE DEVELOPMENT AND COURSE OF THE SYNDROME

Two of the eighty-one patients had been examined five and ten years previous to the onset of retinitis for minor complaints, and hypertension or other abnormal cardiovascular lesions were not found. Four patients on previous examinations made within periods of three, five and seven years of admission revealed definite benign hypertension, but no retinitis. The longest record of hypertension was thirteen years, with retinitis typical of malignant hypertension demonstrable for the last four years.

10 Peabody, F. W., Meyer, A. L., and DuBois, E. F. The Basal Metabolism of Patients with Cardiac and Renal Disease, *Arch. Int. Med.* **17**: 980 (June) 1916. Boas, E. P., and Shapiro, S. Diastolic Hypertension with Increased Basal Metabolic Rate, *J. A. M. A.* **84**: 1558 (May 23) 1925. Boothby, W. M., and Sandiford, Irene. Laboratory Manual of the Technic of Basal Metabolic Rate Determinations, Philadelphia: W. B. Saunders Company, 1920.

of the patient's life. Such observations suggest that serious uncontrolled hypertension may develop primarily in persons whose cardiovascular systems had previously been normal and secondarily in others who have previously suffered from hypertension and general diffuse arteriosclerosis.

We have endeavored to keep in contact, by periodic examinations or by letter, with these eighty-one patients from the time that malignant hypertension was diagnosed. Fifteen of the patients returned for further examinations. Three of these died in Rochester. It was from the data collected in these fifteen cases that we are able to trace the course of the disease. As we noted previously, the cases group themselves into the cerebral, cardiac, renal and combined types.

Cerebral Type—A typical example of this group (case 69, tables 1 and 2) was followed for a period of forty-four months from the time the diagnosis of malignant hypertension was made. During the first two years of our observation, the woman had attacks of numbness in the left arm and leg, with mild disturbance of speech. Later, weakness and numbness of the right leg were manifested. Two weeks before death, she had another apoplectic stroke, as the result of which death occurred in coma. Four months before death, renal function was practically normal.

Cardiac Type—In four cases, marked cardiac insufficiency developed. In three cases it was manifested by severe respiratory distress, chronic passive congestion of the abdominal viscera and dependent edema. In one case the disturbance of cardiac function was shown by attacks of pulmonary edema and nocturnal attacks of Cheyne-Stokes respiration. In all of these cases there was slight renal insufficiency which was probably caused by chronic passive congestion and renal arteriosclerosis. Before the termination of the disease stupor and coma intervened, but the cerebral manifestations were not typical of those seen in the so-called uremic states.

Renal Type—In three cases severe renal insufficiency developed between the time of the first and second examinations. Two of these patients died while under observation in the hospital, the third died one month after leaving the hospital. The maximal blood urea was 152 mg., the maximal blood creatinine, 9 mg., and the minimal phenolsulphonphthalein excretion 10 per cent. With these three cases should be considered two in which severe renal insufficiency was present at the time of the first admission. Death occurred in the hospital, the blood urea being 101 and 144 mg. and the creatinine 4.5 and 7.1 mg., the clinical picture was similar (table 6). The important feature in these five cases is the mild anemia, or absence of anemia, even though the renal insufficiency was of a severe grade. This is explained by the short duration of the renal

TABLE 6—Studies of Renal Function in Fifteen Cases in Which There Were Two or More Admissions to the Hospital

| Blood | | | | | | | | | | Urine | | | | | | | Chloride Test, Percentage Concentration |
|-------|-------|------------------------------------|------------------------------------|--------------------------------|-------------------------|------------------------------------|---------------------------------|------------------|-------------------------|------------------------|--------------------|--|------------------------|---------------------|--------------------|---------------|---|
| Case | Date | Hemo- globin, Gm per Cent | Hemo- globin, gm per Cent | Erythro- cytes, Millions | Urea, Mg per Cent | Creat- inine, Mg per Cent | Uric Acid, Mg per Cent | Specific Gravity | | Albu- min- Grade | Crystals, Grade | Phenol- sulphon- phthalen, per Cent | Water Output, Cc | Before Injection | After Injection | | |
| | | | | | | | | Vari- ation | With Con- centration | | | | | | | With Water | |
| 3 | 3/17* | | | | | | | | | | | | | | | | |
| | 11/22 | 76 | | 4.58 | 32 | | 3.2 | 1 002-1 031 | 1 028 | 1 | 0-1 | 50 | 1,005 | | | | |
| | 11/23 | | 16.5 | | 22 | 1.7 | 2.4 | 1 002-1 027 | 1 027 | 0-1 | | 55 | 1,025 | 0.7 | 2.3 | | |
| 5 | 4/25 | 75 | 16.9 | 4.21 | 31 | 1.3 | | 1 005-1 028 | 1 028 | 0-1 | | 40 | | | | | |
| | 9/21 | 76 | | 4.60 | 29 | 1.6 | 3.1† | 1 001-1 027 | 1 027 | 1-3 | 1-3 | 60 | 1,145 | | | | |
| | 2/22 | | | | 38 | | 3.9 | 1 004-1 028 | 1 028 | | | 45 | 1,540 | | | | |
| 69 | 4/23 | 76 | 14.8 | 4.10 | 24 | 1.6 | 3.2 | 1 010-1 029 | 1 024 | 0-Tr | | 35 | | | | | |
| | 2/25 | 80 | 13.8 | 4.25 | 31 | 1.4 | 2.8 | 1 017-1 025 | 1 025 | Tr | Occasional | 40 | 1,180 | | | | |
| | 10/25 | 76 | 16.8 | 4.41 | 41 | 1.6 | | 1 000-1 020 | | 1 | | 80 | | | | | |
| | 5/26 | 70 | | 4.64 | 31 | 1.1 | | 1 012-1 017 | | Tr | Occasional | 80 | | | | | |
| | 7/26 | | | | 29 | 1.5 | | 1 013-1 026 | | | | 80 | | | | | |
| 61 | 9/25 | 77 | 12.3 | 4.18 | 16-19 | 1.1 | | 1 010-1 022 | | 1 | | 80 | | | | | |
| | 3/26 | 68 | | 3.88 | 22 | | | | | 1 | | | | | | | |
| 61 | 3/24 | 72 | 13.6 | 4.46 | 26-34 | 1.4-1.6 | 3.5-4.5 | 1 002-1 024 | 1 024 | 1 | 1 | 45 | 1,375 | | | | |
| | 2/25 | 80 | | 4.90 | 21-44 | 1.4 | | 1 002-1 021 | 1 002 | 1 | | 50 | 1,860 | | | | |
| 68 | 7/25 | 80 | 15.0 | 4.20 | 18 | 1.9 | 3.3 | 1 000-1 025 | 1 020 | 0-Tr | Rare | 60 | 1,325 | | | | |
| | 7/26 | 68 | 14.3 | 3.90 | 29-40 | 1.9 | | 1 007-1 020 | | 1-2 | | 45 | | | | | |
| 36 | 11/25 | 70 | 13.8 | 3.83 | 30-34 | 1.7 | | 1 010-1 020 | | 1 | 2 | 40 | | | | | |
| | 4/26 | 75 | | 4.36 | 33 | 1.6 | | 1 011-1 016 | | | | 35 | | | | | |
| 35 | 7/25 | 84 | 19.3 | 5.22 | 15 | 1.3 | 4.2 | 1 010-1 021 | 1 021 | 0-2 | 1 | 50 | | | | | |
| | 12/25 | 85 | | 5.68 | 36-45 | 2.1-2.3 | | 1 001-1 022 | | 2-3 | 2 | 20 | | | | | |
| 19 | 7/23 | 73 | | 4.74 | 22 | | | | | | 1 | 35 | | | | | |
| | 11/23 | | | | 10 | 2.2 | 4.8 | 1 005-1 020 | 1 020 | 1 | 1 | 30 | | | | | |
| 40 | 5/25 | 82 | | 4.72 | 30-36 | | | 1 005-1 025 | 1 025 | 1-2 | Occasional | 37-40 | 840 | | | | |
| | 8/25 | 68 | 11.2 | 3.79 | 46 | 2.0 | | 1 002-1 028 | 1 028 | 1 | Occasional | 45-55 | 710 | | | | |
| 53 | 3/22 | 75 | | | 26 | | | 1 003-1 030 | 1 030 | 1 | Rare | 20 | 1,450 | | | | |
| | 5/26 | 71 | | 3.88 | 33-35 | 1.8-2.2 | 3.9 | 1 003-1 017 | 1 017 | 1 | | 40 | | | | | |
| 55 | 4/25 | 70 | 14.8 | 4.01 | 24-35 | 1.6 | | 1 010-1 030 | | 1-2 | | | | | | | |
| | 7/25 | | | | 28-34 | | | 1 006-1 012 | | 1-3 | | | | | | | |
| 65 | 6/25 | 71 | 17.9 | 4.02 | 34 | 1.4 | 3.4 | 1 003-1 025 | 1 025 | 1 | Occasional | 45 | 1,055 | | | | |
| | 7/26 | 68 | | 4.30 | 34-43 | 1.7-2.5 | | 1 002-1 030 | 1 030 | Tr | | 50 | 685 | | | | |
| | 9/25 | 71 | 15.9 | 4.04 | 35-108 | 3.1-6.8 | | 1 003-1 011 | | 1-2 | Rare | 25 | | | | | |
| 66 | 12/23 | 76 | | 4.71 | 33 | 1.8 | | 1 009-1 018 | | 1-2 | Rare | 40 | | | | | |
| | 9/24 | 70 | 13.2 | 4.00 | 91-134 | 3.9-7.4 | 3.6-4.6 | 1 015-1 016 | | 2-3 | 1 | 30 | 975 | | | | |
| | 3/25 | 73 | | 4.20 | 33-40 | 2.0 | | 1 001-1 023 | 1 001 | 1-2 | Rare | 1-2 | | | | | |
| | 2/26 | 66 | | 3.93 | 67-152 | 5.7-4.6-9.0 | | 1 001-1 017 | | 1-2 | Rare | 10 | | | | | |

* Examination five years previous to diagnosis of malignant hypertension
† Blood uric acid, Folin and Wu method J Biol Chem 38 81, 1919

| Case | Gross | Heart | | Coro- nary Sclero- sis Grade | Kidneys (com- bined Weight Gm) | Brain | Sclerosis of Arter- ies (Grade) | Microscopic Changes | | | Opticnalmic, Grade | Smaller Vessels, Grade |
|------|-------|--------------|------------------------------------|--|--|--|---|--|---|--|--|--|
| | | Weight Gm | Myo- cardial Change Grade | | | | | Cardiac Grade | Renal, Grade | Cerebral Grade | | |
| 26 | | 715 | | 2 | 124 | | | Sclerosis of arteries, 3 | Chronic diffuse nephritis, arterio- sclerosis, 2, sclero- sis of arterioles, 1 | | | Generalized sclerosis of arteries, 1 |
| 27 | | 570 | Litho- sis, 1 | 1 | 66 | | | Sclerosis of arteries, 3 myocardial fibrosis, 3 | Chronic diffuse nephritis, arterio- sclerosis, 3, sclero- sis of arterioles, 1 | | | Generalized sclerosis of arteries, 1 |
| 27 | | 400 | | 2 | 270 | Areas of softening and of hemorrhage | 1 1 | Sclerosis of arteries, 3, fibrosis of myo- cardium, 1 | Chronic diffuse nephritis, arterio- sclerosis, 2, sclero- sis of arterioles, 1 | Arteriosclerosis, 3, sclerosis of arteries, 1, areas of softening and hemorrhage | | Generalized sclerosis of arteries, 1 |
| 45 | | | | | | | | Chronic diffuse nephritis, arterio- sclerosis, 3, sclero- sis of arterioles, 3 | | | | Generalized sclerosis of arteries, 4 |
| 60 | | 585 | Litho- sis, 2 | | 332 | Areas of softening and of hemorrhage | 3 | Hypertrophy of myocardium and fibrosis and sclerosis of arterioles, 3 | Arteriosclerosis, 3, sclerosis of arteries, 1, chronic diffuse nephritis | Arteriosclerosis, 1, sclerosis of arteries, 2, areas of softening and multiple areas of hem- orrhage | Sclerosis of arteries of choroid, 1, and of retina, 2, areas of hemorrhage and exudates | Generalized sclerosis of arteries, 4 |
| 80 | | 496 | Litho- sis, 1 | 3 | 206 | Areas of softening and of hemorrhage | 2 1 | Slight hyper- trophy of fibrous and sclerosis of arterioles, 2 | Arteriosclerosis, 3, sclerosis of arteries, 4, chronic diffuse nephritis | Arteriosclerosis, 1, sclerosis of arteries of ves- sels of subarach- noid space and brain, 2, areas of softening and hemorrhages | Sclerosis of arteries of choroid, 1, and of retina, 2, areas of hemorrhage and exudates | Generalized sclerosis of arteries, 4 |
| 81 | | 570 | Fibrosis, 2 1 | 1 | 325 | Areas of softening and old small areas of hemorrhage | 2 | Hypertrophy of myocardium and fibrous and fibrous 2+, sclerosis of arterioles, 2 | Arteriosclerosis, 3, sclerosis of arteries, 4, chronic diffuse nephritis | In subarachnoid vessels arterio- sclerosis, 2, sclero- sis of arterioles, 2 In brain arterio- sclerosis, 2, sclero- sis of arterioles, 1 | Sclerosis of arteries of choroid, 4, and of retina, 1, areas of hemorrhage and exudates | Generalized sclerosis of arteries, 1, also in skeletal muscles |

insufficiency, which is in marked contrast to the extent of renal insufficiency and secondary anemia seen in the last stage of chronic glomerulonephritis

From the course and terminal picture of this syndrome we have abundant evidence that death is not due to the failure of any vital organ but to a severe widespread disease

Combined Type—Case 65 (table 1) is a typical example of this group. A man, aged 46, was first examined in June, 1925. For three years, the blood pressure had been elevated, he had been nervous and slightly dizzy at times and had suffered from frequent occipital headache. For five weeks before examination, vision in the right eye had been poor.

On examination, the patient seemed nervous and slightly apprehensive. He was large and apparently healthy, weighing 182 pounds (82.7 Kg). The peripheral arteries were apparently sclerosed (graded 1). The heart was moderately enlarged, measuring 3.5 cm. to the right and 13.5 cm. to the left. Definite tachycardia was present, but no murmurs or other abnormal heart sounds were heard. Dyspnea, edema and anemia were not present. The systolic blood pressure was 240 and the diastolic, 145. The Wasseimann test with the blood was negative. The electrocardiogram showed inversion of the T wave in lead I. The basal metabolic rate was +7 and +15 on two occasions. The thyroid gland was not definitely abnormal. Ophthalmoscopic examination showed edema of the disk and retina, which was more severe in the right eye, apparent sclerosis (graded 3) of the retinal arteries, scattered hemorrhagic areas and cotton-wool and punctate exudates. The urine contained albumin (graded 1) and an occasional hyaline cast. The phenol-sulphonphthalein output was 45 per cent in two hours and the water output 1,055 cc. in four hours. The specific gravity of the urine varied from 1.003 to 1.025. In the blood, the urea was 28 mg., creatinine, 1.4 mg., and uric acid, 3.4 mg. for each hundred cubic centimeters. Here, then, was a case characterized by high blood pressure, absence of anemia, good cardiac function (except for the inverted T wave in lead I) and practically normal renal function, in which the retinal changes indicated a serious prognosis. While the patient was in the hospital, the blood pressure was reduced after a therapeutic bath to 200 systolic and 110 diastolic and, after ingestion of sodium nitrite, to 160 and 110, respectively. After two weeks of treatment, however, the systolic blood pressure was still 230 and the diastolic, 130.

Thirteen months later, the patient was admitted for the second time. He had been able to carry on his work during the intervening period, but was in much the same condition as on his first admission, both as to symptoms and physical condition. The systolic blood pressure was 240 and the diastolic, 150. The condition of the retina was unchanged, but

the electrocardiogram was negative. The blood count was not changed. The basal metabolic rate was $+14$ and $+20$ on two occasions. The blood pressure fell after a hot bath to 220 systolic and 120 diastolic, and after the ingestion of sodium nitrite to 175 and 120, respectively, it was not affected by phenobarbital. There was a trace of albumin but no casts in the urine, the specific gravity ranged from 1.002 to 1.030, the water output was delayed (685 cc), the blood urea was from 34 to 43 mg and the blood creatinine, from 1.7 to 2.5 mg for each hundred cubic centimeters. Summarizing, the blood pressure was high and unchanged, the retinal picture was the same, no abnormality was disclosed by the electrocardiogram, slight renal insufficiency was indicated by the level of the blood urea and by diminished output of water. Although practically there had not been any change in the patient's general condition during the year, the retinal changes still made us feel that the prognosis was grave.

Five weeks later, in September, 1926, the patient was admitted to the hospital for the third time. For three weeks, he had been suffering from nausea and vomiting. At the time of examination he was nervous. The systolic blood pressure was 220 and the diastolic, 140. Anemia was not present. The edema of the disks and retina was slightly increased, and a number of fresh cotton-wool exudates and hemorrhagic areas were present. There was definite evidence of serious renal insufficiency, the blood urea being 85 mg, the creatinine, 3.1 mg, and the phenolsulphonphthalein excretion, 25 per cent. While the patient was in the hospital, the renal insufficiency became more marked and at times attacks of pulmonary edema occurred. One month later, in October, 1926, the patient died, cardiac and renal failure being the immediate cause of death. He had been delirious and comatose for forty-eight hours before death. The blood urea had risen to 108 mg and the creatinine, to 6.8 mg. Permission for necropsy was not obtained.

This patient had known of the presence of hypertension for approximately four years. It is certain that the malignant type of hypertension had been present for sixteen months, yet it is significant that for thirteen of the sixteen months he enjoyed comparatively good health. Then rapid renal, cardiac and cerebral failure occurred, indicating the termination of a diffuse pathologic process.

Of the eight patients in this series who died in Rochester, the terminal illness was of the combined type in five, cerebral in two, and cardiac in one.

HYPERTENSION

The degree of hypertension was studied in each patient in the hospital. We observed the reaction of the heightened blood pressure to rest in bed, hot baths and the periodic use of sodium nitrite, phenobarbital and typhoid vaccine. After these measures, there was usually a tem-

porary fall of blood pressure. The actual minimal blood pressure obtained in this series was 140 systolic and 60 diastolic, following the ingestion of sodium nitrite. After phenobarbital was given, the minimal figures were 150 and 95, after a hot bath, 140 and 85, and after typhoid vaccine, 170 and 100. The rule in these cases was that the blood pressure continued at a high level despite the temporary falls. On admission, the diastolic blood pressure in seventy-two cases was above 120 mm. On dismissal, the diastolic pressure in forty-six cases still continued to be above 120 mm. That it is nearly impossible to lower the blood pressure permanently in these cases by our present therapeutic methods is clearly shown by the fact that, in forty-two of the present series, diastolic pressure was never reduced by any measures below 110 mm.

THE RETINA¹¹

The retinitis is graded 1 to 4 on the basis of the amount of papilledema, the degree and extent of the retinal edema, the number of cotton-wool exudates and hemorrhagic areas and, in the later stages, the number and extent of exudates associated with absorbing edema, and the completeness and density of the macular star.

The grade of the retinitis refers to the severity of the retinal lesions. A retinitis of any grade has a definite course of development from onset to resolution, which is independent of its severity. This course is divided into four stages by definite differences in the appearance of the retinal lesions, the dividing lines of which, it is true, are not absolutely differentiated. Detailed data in each case are included in table 1.

A more detailed description of the ophthalmoscopic and histologic features of the retinitis of malignant hypertension with a discussion of its clinical significance was presented as a thesis to the American Ophthalmological Society and will be found in the transactions of the society for 1927.

The type of the retinitis and not its severity is characteristic of this group of cases. Edema of the disks is a striking feature in all the cases and is often disproportionate to the other retinal changes. All grades of the retinitis, from the mildest to the most severe, run a characteristic course which may be divided into four stages. In the first stage, hyperemia and mild edema of the disk and peripapillary retina, with a few superficial hemorrhagic areas and cotton-wool exudates, are present. In the second stage, the edema of the disk and retina becomes more marked and spreads into the macular region and periphery, the hyperemia continues, the hemorrhagic areas and cotton-wool exudates become more numerous and are found farther away from the disk and

11 The sclerosis of the retinal arterioles is graded 1 to 4 on the basis of the degree of constriction in caliber, of increased brightness of the reflex stripe, of the severity of the compression at the arteriovenous crossings, and particularly of the frequency and the extent of localized irregularities in the lumen of the arterioles.

in the deeper layers of the retina as well, a few punctate exudates are seen. In the third stage, the edema begins to recede from the peripheral part of the retina, and small spots of proliferated pigment are seen in its stead. Punctate exudates begin to outnumber the cotton-wool exudates, and arrange themselves into imperfect star figures in the macular region. The hemorrhagic areas are relatively fewer and are, in the main, more peripherally situated. The hyperemia of the disks is less evident and may gradually fade. As the retinitis progresses through these stages the associated sclerosis of the retinal arterioles becomes more marked due partially to perivascular thickening and gliosis caused by edema of the surrounding retina. In the fourth stage, the disk has become definitely pale and only blurring and increased glial tissue remain as evidence of the previous edema (secondary atrophy). Definite perivascular thickening along the walls of many of the vessels, the veins as well as the arteries is seen. Atrophy has replaced edema of the retina, and only a few residual small punctate exudates may remain, usually in the macular region. Spots of proliferated pigment are numerous, especially in the macula and periphery. Patchy sclerosis of the choroidal arteries is noticeable. An occasional small hemorrhagic area may be present (figs 2 and 3).

It is difficult to estimate the duration of the various stages of the retinitis, as we have not been able to follow any one case continuously through all stages. On the basis of subjective visual complaints, the retinitis had existed for an average of four months in the cases observed in the second stage. In those in which the retinitis was in the third stage it had existed for an average of six and a half months. The retinitis in one patient had progressed from the first to the second stage by the end of four months. In another it had progressed from the second to the third stage by the end of two and a half months, and in one from the first to the third stage by the end of one year. In two cases in which at first observation the retinitis was in the second stage, it had advanced to the third stage a year later. In one case, the retinitis had progressed from the third to the fourth stage after eleven months. Apparently the first stage is the shortest or has the least effect on vision, patients having been seen in whom the retinitis was definitely in the second stage one week after the onset of visual disturbances. The third stage is the longest and the most frequently observed. In one case, the retinitis was still in the third stage at least forty months after the onset. In the case manifesting the most definite fourth-stage retinitis, the disease had started about three years previously.

In sixteen cases it was possible to observe the course of the retinitis at intervals for a considerable period. In six cases the retinitis progressed in stages but maintained about the same grade of severity during the period of observation. In six other cases the retinitis

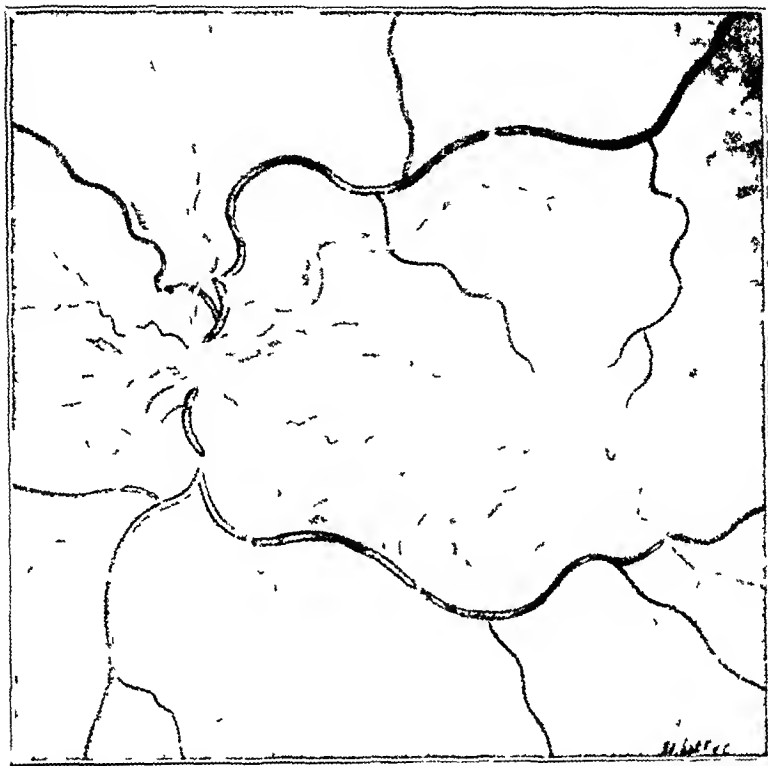


Fig 2—Retinitis (stage 2 to 3) of malignant hypertension (diagram)



Fig 3 (case 81)—Posterior half of eye, showing edema of optic disk, hemorrhages and exudates, $\times 25$

progressed in both stage and grade. The sclerosis of the arterioles especially showed a definite tendency to increase in grade. The retinitis regressed in only four cases. One mild case of retinitis subsided completely before the patient's death, and left only vascular residuals. Typical fourth-stage retinitis with secondary optic atrophy was seen in only one case, cerebral decompression had been performed elsewhere for suspected tumor of the brain. Whether this operation was a factor in accelerating the resolution of the retinitis is difficult to say. It is interesting in this connection, however, to recall that Cushing and Bordley¹² think that increased intracranial pressure, with resultant increased fluid pressure in the intervaginal spaces of the sheath of the optic nerve, is a factor in causing the edema of the disk and retina in the retinitis of nephritis. Three cases of typical retinitis and moderate to severe sclerosis of the retinal arterioles had been observed from two to six years previously, at which time the mild arterial change was the only abnormality in the retina. In two cases in which mild retinitis of the type of benign hypertension had once been observed, retinitis of malignant hypertension was found later.

PROGNOSIS

The seriousness of this disease is shown by the fact that of the eighty-one patients, seventy-four (91 per cent) died within fifty-one months, the majority within two years. Only five patients lived two years or longer. The average length of life after diagnosis was eight months. Our data concerning the terminal illness is somewhat meager. Sixty-six patients died at home, and the physicians recorded only the chief cause of death. A few, however, described the course of events, which was similar to that in the eight cases we had observed.

PATHOLOGIC DATA

A postmortem examination was made in seven cases. Four of these examinations were fairly complete, two only partially so, and one was carried out elsewhere, only sections of the kidney being sent for microscopic examination. The detailed changes noted grossly and microscopically are given in the tables. The following description is a summary of the pathologic data in cases 26, 32, 37, 45, 66, 80 and 81 (table 7).

The gross changes are really not characteristic, and only a few were constant throughout. Edema may be absent but when present varies much as to site and extent. The heart is always hypertrophied, but the degree is not constant, in the cases in which there is a long history of hypertension there is usually a high degree of cardiac hypertrophy, while,

¹² Cushing, Harvey and Bordley, James. Subtemporal Decompression in a Case of Chronic Nephritis with Uremia, with Especial Consideration of the Neuroretinal Lesion, *Am J M Sc* **136** 484, 1908.

when the history is short, the hypertrophy is of lesser degree. Coronary sclerosis is usually graded 2 and apparently is not dependent on the cardiac hypertrophy or on the age of the patient. Sclerosis of the aorta also varies in degree in different cases, the average being slightly less than grade 2. There is nothing constant about the changes in the kidneys, although they usually show evidences of arteriosclerosis, sometimes they

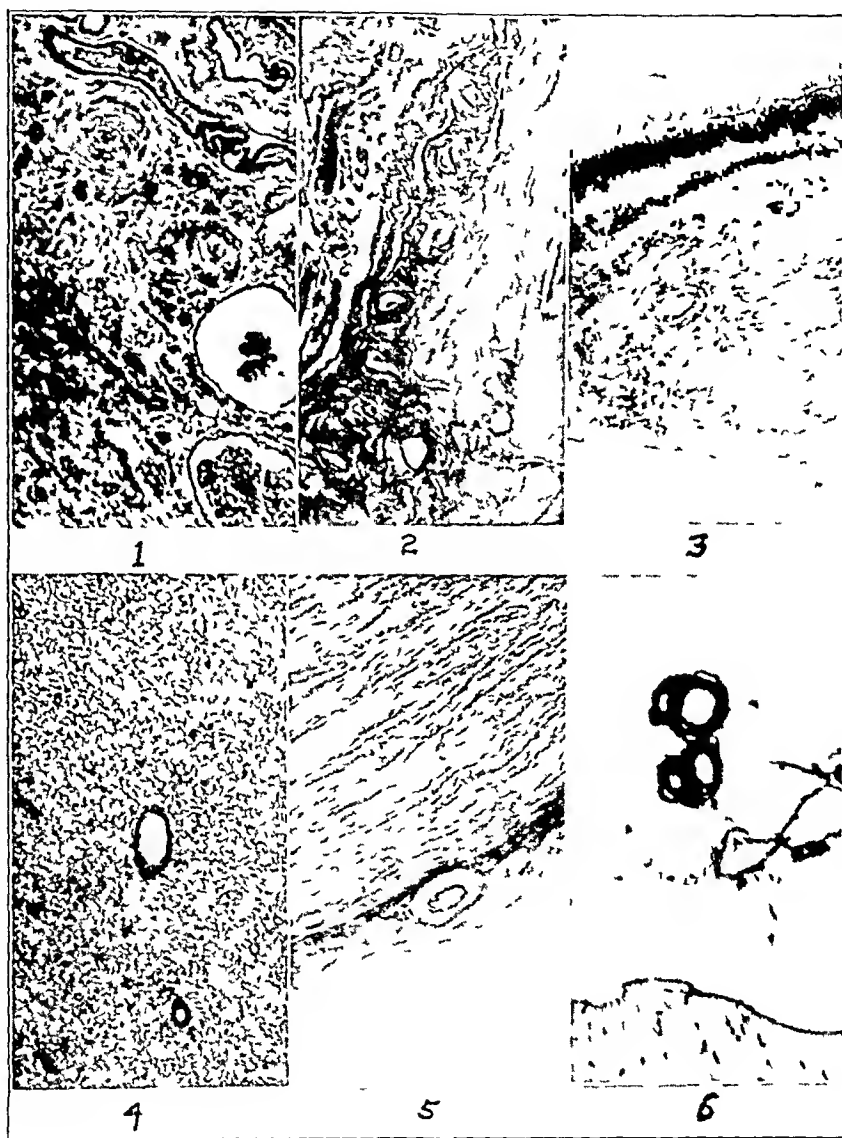


Fig. 4 (case 81)—Arteries from various organs: 1, kidney; 2, skeletal muscle; 3, retina; 4, brain; 5, choroid; 6, subarachnoid vessels.

are atrophic and shrunken, but more often the combined weight is only slightly less than normal. In the four cases in which the brain was examined, definite evidence of arteriosclerosis was present. The vessels in the subarachnoid space and in the circle of Willis as a rule show mild sclerosis. In the coronal sections of the brain, multiple areas of softening were seen, whether these softened areas are due to minute hemor-

changes or simply to occlusion of vessels is difficult to determine. Occasionally a severe hemorrhage was encountered which had caused definite clinical symptoms and possibly was the immediate cause of death.

In the microscopic studies of the tissues there are several important features: the most outstanding are the diffuseness of the lesions and the degree of involvement of the smaller arteries and arterioles, while the larger arteries and the capillaries are comparatively free from change (fig. 4). The changes in the arterioles are different from those observed in the arteries of old persons: there is more marked hyperplasia of the intima and hypertrophy of the media and internal elastic lamina (fig. 5) in contrast to the degenerative changes in senile arteriosclerosis with

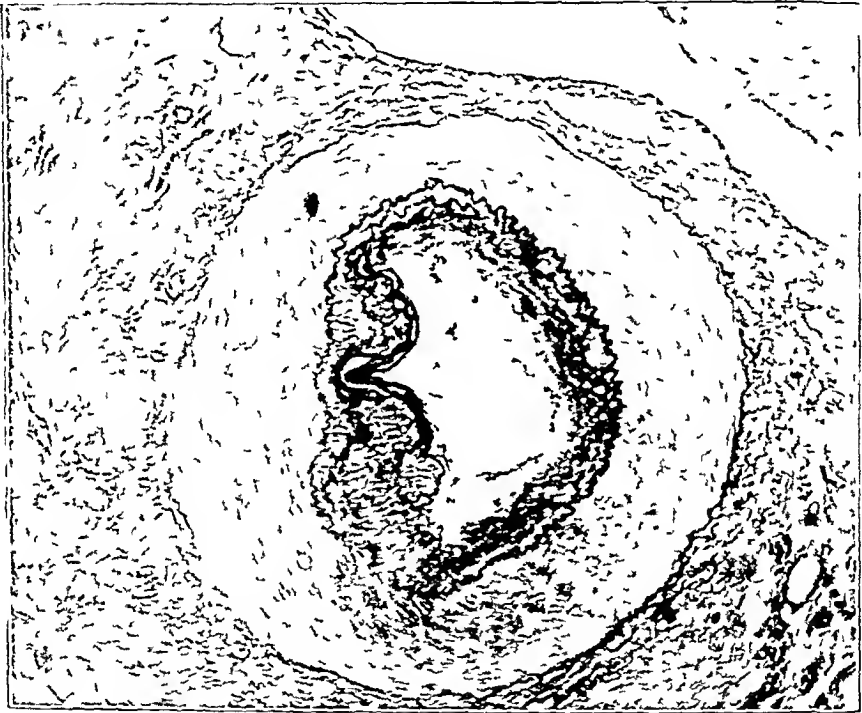


Fig. 5—Small artery of kidney showing thickened media, hypertrophy and splitting up of internal elastic lamina. Narrowing of lumen and perivascular fibrosis. Weigert's elastic tissue stain, $\times 60$.

their deposits of lipoids, fatty acid and calcium in the intima and fragmentation but little hypertrophy of the internal elastic lamina. Again in senile arteriosclerosis the smaller arteries and arterioles do not manifest the extensive intimal hyperplasia and the marked narrowing of the lumina which is so definite in these cases of malignant hypertension. Perivascular fibrosis of varying degrees of intensity is present. Sometimes fibrosis is diffuse throughout the organ, while in the brain the diminution of the blood supply causes softening and formation of cysts (fig. 6) rather than gliosis. These areas of softening in the brain are not limited to any one region but are usually scattered more or less diffusely through-

out the organ, although they may be more severe in one area than in others. These collected areas of softening vary in situation in different cases, but they are not particularly evident in the floor of the fourth ventricle or around the aqueductus cerebri, nor is the sclerosis of the arterioles more marked in these areas. An interesting but unexplained observation is that the degree of vascular obstruction is much milder in the retinal vessels (figs 7 and 8) than in the choroidal vessels (figs 7 and 9) and also that it is less in the vessels of the subarachnoid space than in the vessels supplying the brain substance proper. Thus the retinal and subarachnoid vessels are comparable in degree of sclerosis as are those of the choroid and the brain.

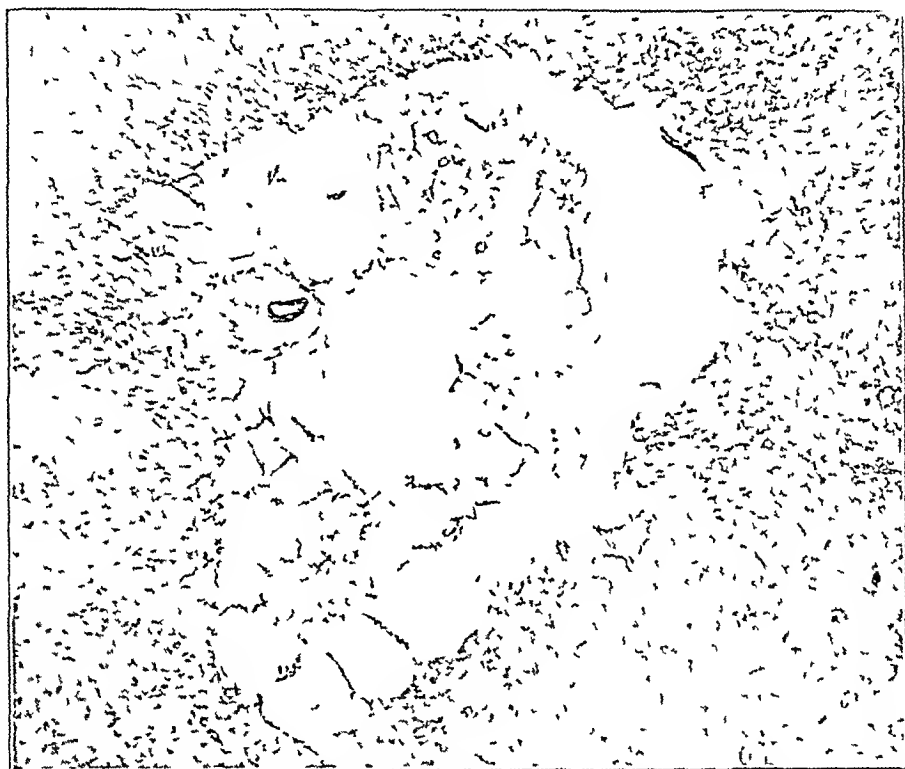


Fig 6—Area of softening in the brain. The small artery in the center is not occluded as a result of either sclerosis or thrombosis. Hematoxylin and eosin, $\times 30$.

Throughout the retina but especially around the disk and the macula, considerable numbers of homogenous masses that stain with eosin are present. The larger and more recent ones seem to be in the superficial layers of the retina (fig 10), while the smaller, the more numerous and apparently the older ones are in the internuclear layer. The smaller masses are in what appears to be different stages of absorption (fig 7), large phagocytic cells that contain fat are near them, sometimes in the margin and sometimes within the mass, while in some areas little else but these fat cells can be seen (fig 11). The collections of these cells that contain fat suggest that complete phagocytosis of previous

similar masses has taken place. The hemorrhages have a similar distribution to the so-called exudates, large areas of recent hemorrhages are seen in the layers of ganglion cells and nerve fibers (fig 12), while numerous small and older ones are present in the internuclear layer.

The most important and constant feature of these cases is the extreme diffuseness of the lesion, not a single organ or tissue escapes, and even the vessels of the gastro-intestinal tract and the skeletal muscles are equally severely involved (fig 4). Sometimes the kidney, the heart or the brain is more severely injured but not any organ escapes. The

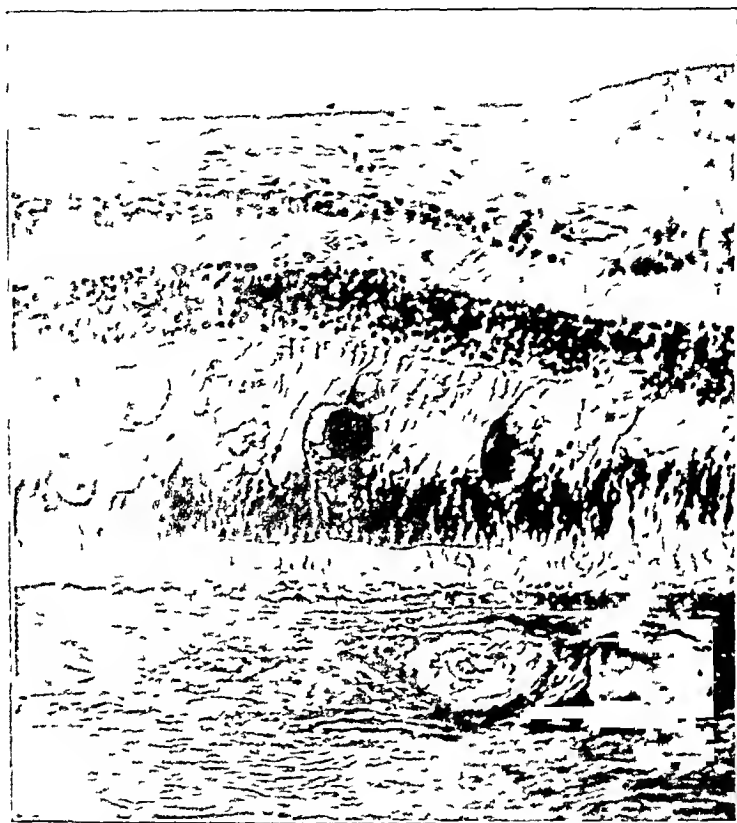


Fig 7—Exudate in the internuclear layer of the retina. Different stages in the process of absorption can be seen. The relative sclerosis in the retinal and choroidal arterioles should be noted. Hematoxylin and eosin, $\times 120$.

kidneys in every case show profound changes, all of which can be attributed to the severe vascular injury chiefly of the smaller arteries and arterioles (fig 13). The capillaries are almost unaffected, except in the glomerular tufts where the nuclei are apparently more numerous. The glomerular tufts themselves show marked changes but they are different from those observed in glomerulonephritis. Some glomeruli are completely fibrosed, others only partly so, as the tuft may be lobulated and one or several lobules fibrosed and the others intact. Some glomeruli are apparently normal and are even hypertrophied, the only change being

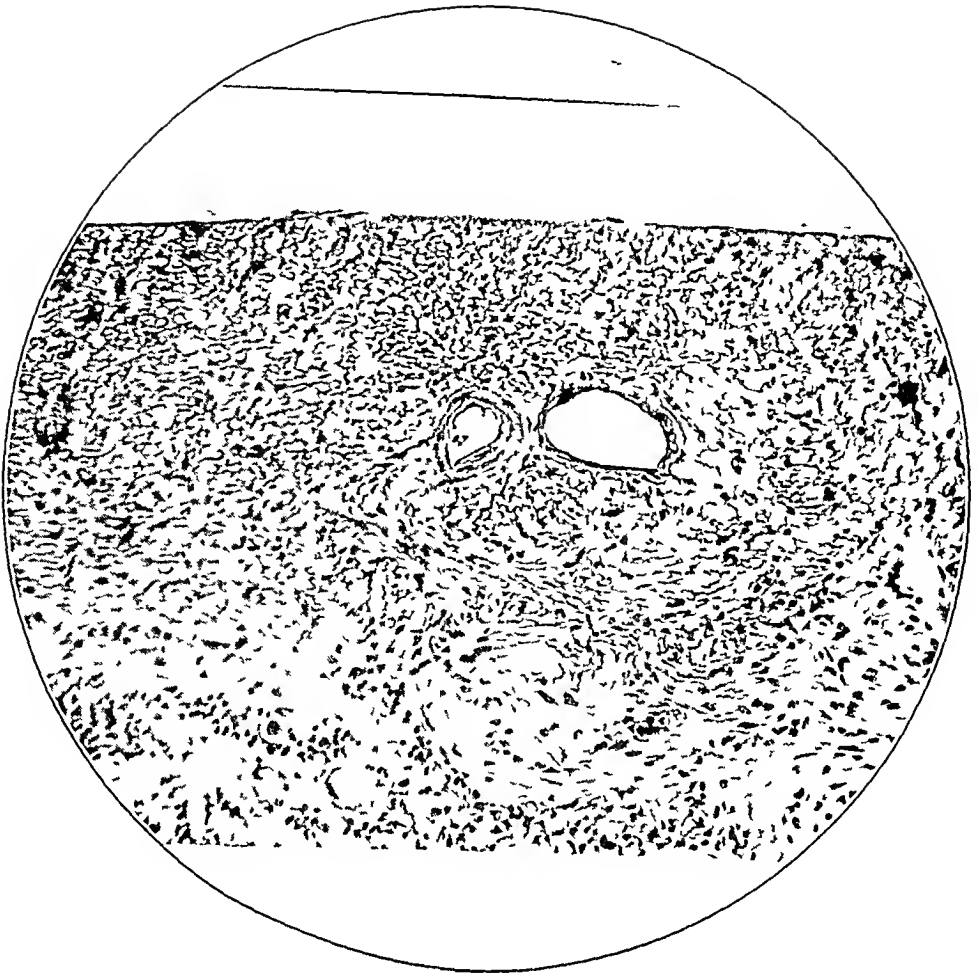


Fig 8—Arteriole and venule of the retina at the optic disk. There is slight thickening of the walls of the arterioles, but it is of a minor degree compared with choroidal arterioles. The edema and the increase in glial tissue also should be noted. Hematoxylin and eosin, $\times 200$.

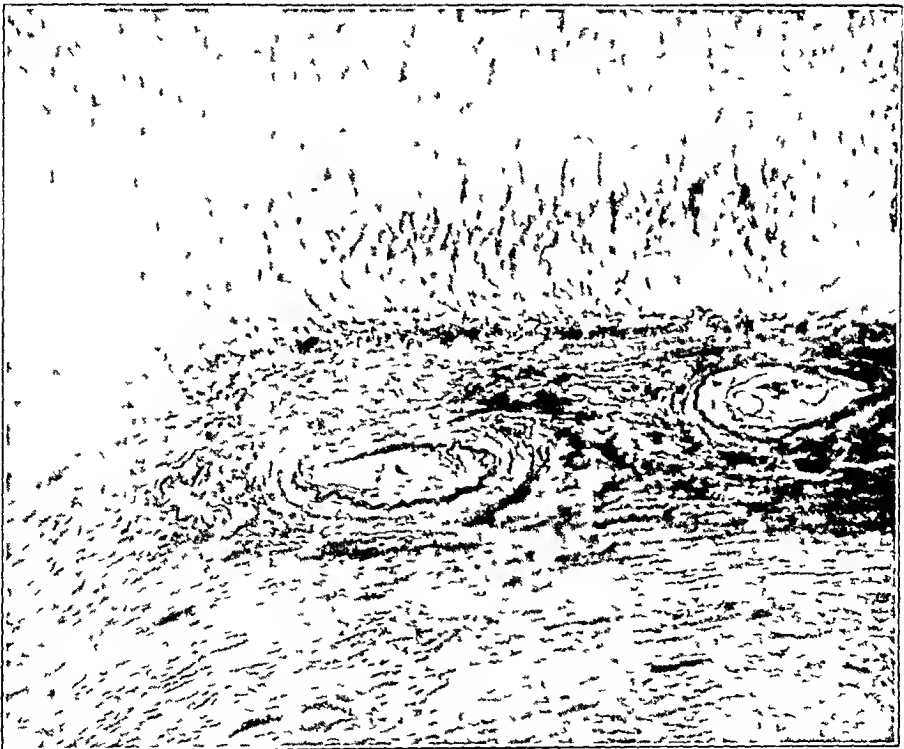


Fig 9—Arterioles of choroid showing thickening of walls, hypertrophy of internal elastic lamina with almost complete occlusion of lumina. Weigert's elastic tissue stain, $\times 120$.

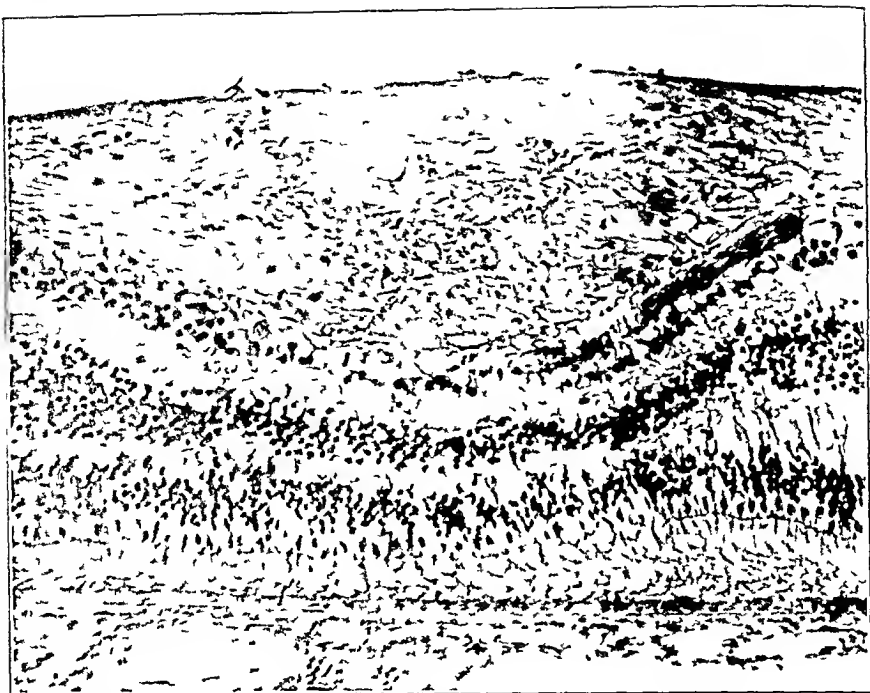


Fig 10—Large exudate and some cytoroid bodies in the layer of nerve fibers of the retina Hematoxylin and eosin, $\times 120$

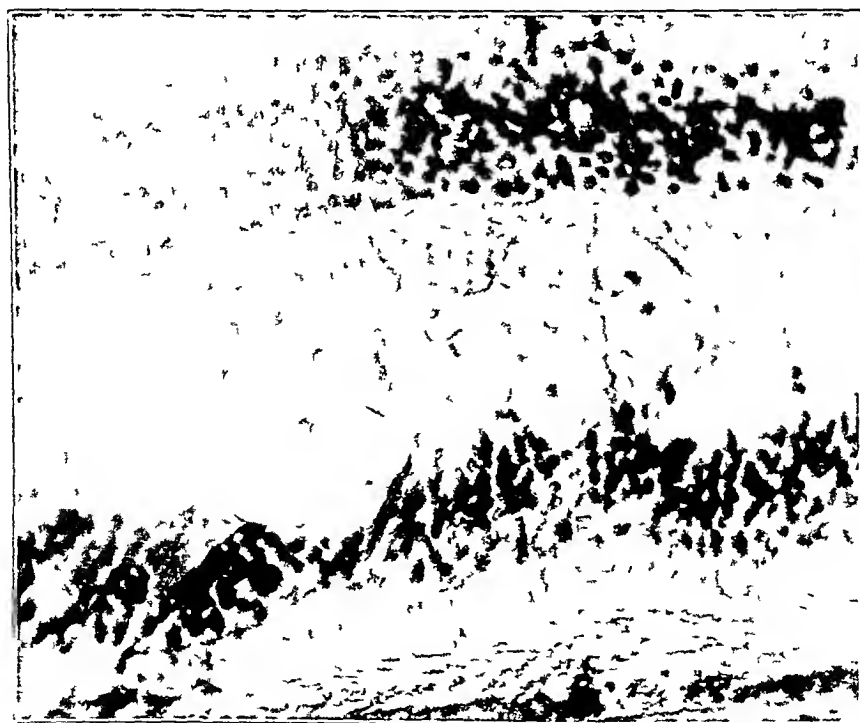


Fig 11—Complete replacement of exudates in the internuclear layer of the retina by large clear "scavenger" cells Hematoxylin and eosin $\times 225$

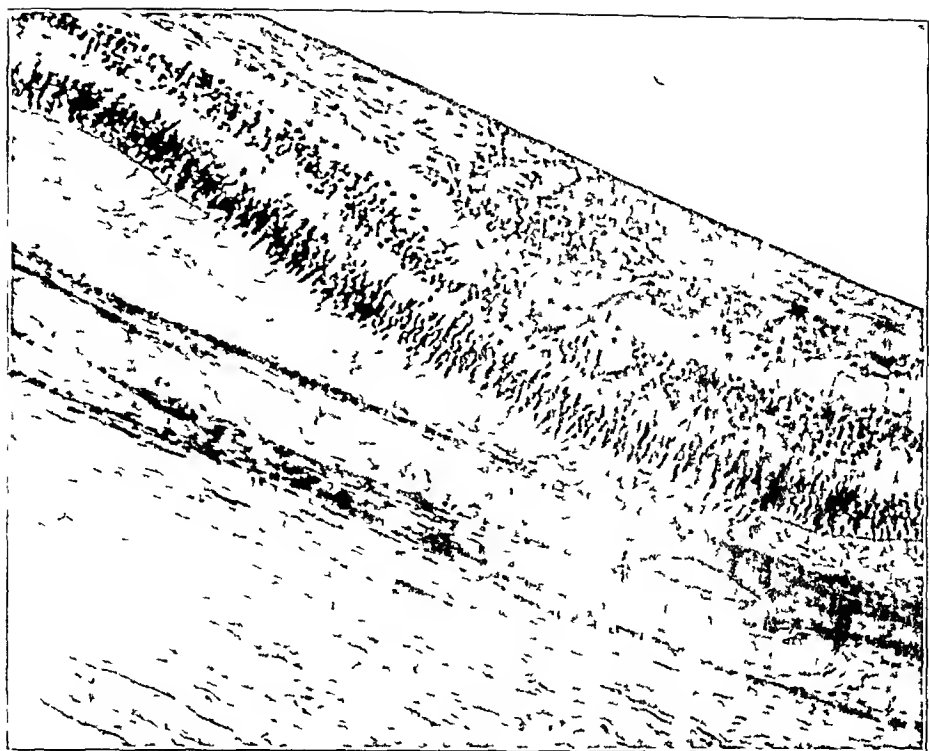


Fig 12—Recent hemorrhage in the layer of nerve fibers of the retina
Homogeneous exudate between retina and choroid Hematoxylin and eosin,
× 100

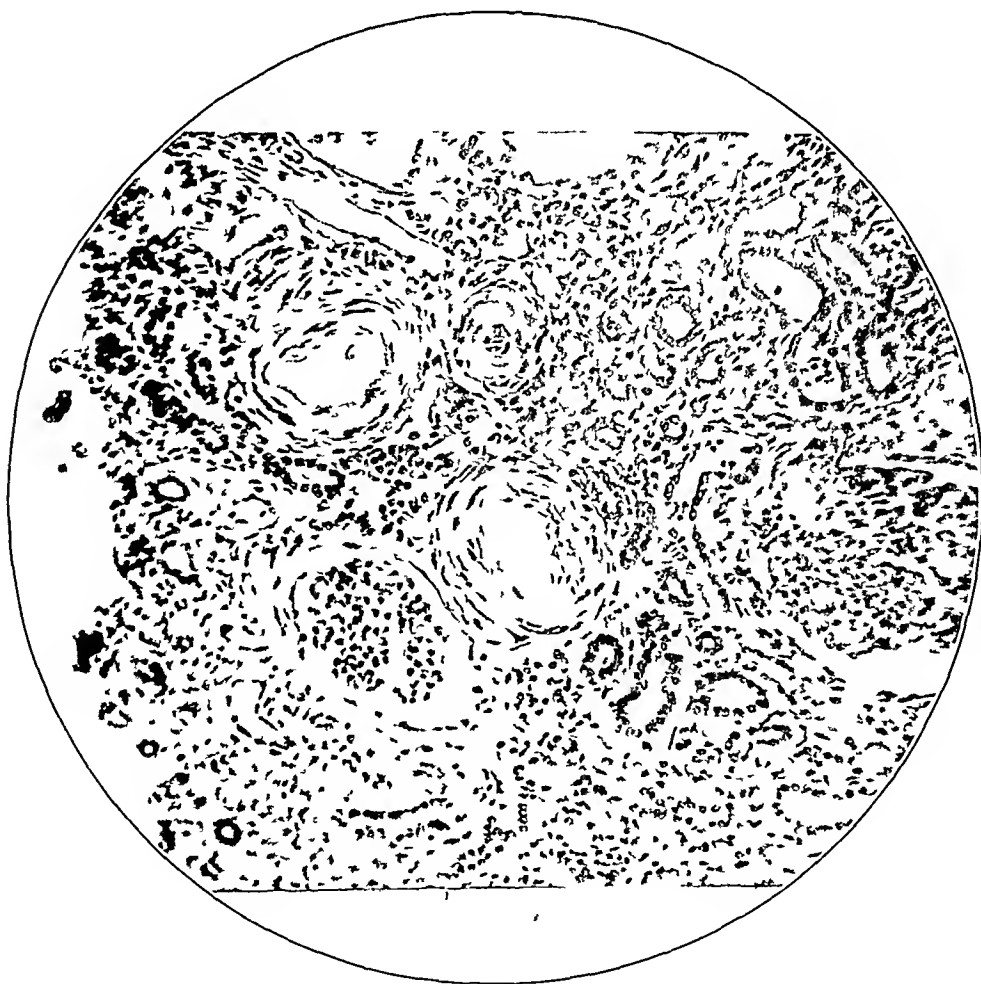


Fig 13—Small arteries and one arteriole of kidney Almost complete occlusion of lumen of the arteriole by the intimal and medial proliferation Arterial walls thickened The comparatively good glomerulus with some increase in the endothelial cells of the tuft should be noted Hematoxylin and eosin, × 200

an apparent increase in the endothelium of the capillaries. Extensive interstitial fibrosis and destruction of some of the tubular epithelium, with little evidence anywhere of true inflammation, are present. All these changes can be attributed to the severe ischemia of the kidney and do not resemble any of the primary diffuse renal lesions.

COMMENT

Owing to the diffuse vascular changes in this disease, the abnormal symptoms will necessarily be varied, and these may or may not be typical of any characteristic syndrome associated with disease of a single organ. We have dwelt particularly on the symptoms arising from cerebral and retinal lesions, and yet frequently these are not especially noted by the patients themselves. The reserve of cardiac muscle may be greatly reduced and yet symptoms referable to a failing heart may be slight or absent. Typical symptoms due to renal disease are infrequent, similarly, evidence of angina pectoris, intermittent claudication, and other peripheral arterial lesions are uncommon, anemia is rare. The vagueness of the symptoms and the paucity of physical defects make one wonder whether simply persistent marked hypertension constitutes a serious disease, yet the course of these cases is truly malignant. Careful consideration reveals further objective signs, the most significant of which is the retinal lesion. The electrocardiogram often reveals disease of the myocardium, renal tests may show minor functional defects, palpation may indicate diffuse sclerotic changes in the arteries, the ophthalmoscope may suggest similar changes in the retinal arterioles, and examination of the capillaries of the nail-fold reveals abnormal blood flow and even contraction and tortuosity. The terminal picture is often obscure and strikingly suggests simultaneous rapid failure of the vital functions of the brain, heart and kidney. Our pathologic data confirm the observations that this syndrome is associated with extremely diffuse arterial disease.

Allbutt,¹³ Janeway¹⁴ and others have reported many cases of patients having benign hypertension or hyperpiesia. They followed the course for several years and have shown that these patients may live comfortably to old age. Renal, cardiac, cerebral and retinal functions remain adequate. Since the time of Bright,¹⁵ diffuse vascular disease

13 Allbutt T. C. An Address on Arteriosclerosis and the Kidneys, *Brit M J* **1** 853 and 922, 1911, Diseases of the Arteries, Including Angina Pectoris, New York, The Macmillan Company, 1915, p. 10.

14 Janeway, T. C. Nephritic Hypertension. Clinical and Experimental Studies. *Am J M Sc* **145** 625, 1913.

15 Bright Richard. Albuminous Urine of Four or Five Years Continuance, Death with Convulsions and Apoplexy. Kidneys Degenerated, *Guy's Hosp Rep* **1** 358, 1836.

has been recognized in association with chronic glomerulonephritis. Distinctive features of this disease, besides hypertension, are anemia, severe renal insufficiency, retinitis and a progressive downward course. Malignant hypertension can be distinguished from the benign form by the persistently high blood pressure and the rapid course. It may arise apparently *ipso facto*, particularly in the young, but frequently it is a later stage of the benign type. The course in both malignant hypertension and chronic glomerulonephritis may be stormy and rapidly fatal, but there are many dissimilar features. Anemia and renal insufficiency that are so characteristic in the one may be absent in the other. We believe that the retinitis can often be differentiated. In malignant hypertension the edema of the retina is less extensive and less dense, and there is little tendency to the formation of peripapillary snow-bank exudates. Edematous detachment of the retina was seen in only one case in the present series. The hyperemia of the disk is in marked contrast to the anemia of the disk and the retina that is seen in the retinitis of nephritis. Sclerosis of the retinal arterioles is always present in malignant hypertension and is usually absent in chronic nephritis. It is interesting that as long ago as 1884, Michel¹⁶ recognized the serious prognostic import of retinitis in cases of chronic nephritis. Some of his patients in all probability had malignant hypertension, though the cases were not so differentiated by him. A definite relationship is not evident between the severity of the retinitis of malignant hypertension and the degree of impairment of renal function. Severe retinitis occurs with adequate renal function and without retention of urea. However, retention of urea is more often present when the retinitis is severe than when it is moderate. We believe that there are patients who have potentially malignant hypertension in whom retinal arteriosclerosis alone is evident or in whom arteriosclerosis with hemorrhages and exudates is present, but no edema of the disk. In the present series, however, only the cases in which definite papilledema was evident are included.

In the development of chronic glomerulonephritis, the kidney is severely injured and impairment of renal function occurs early. Hypertension develops gradually, and vascular fibrosis may be a late manifestation. This is particularly true in the retinal arterioles. On the other hand, at the onset of malignant hypertension, renal impairment may be difficult to demonstrate and develops only in the terminal stages, while changes in the arterioles appear early, especially in the retina. Thus, in malignant hypertension the renal involvement appears to be secondary to vascular lesions which are common to many viscera. Moreover, chronic glomerulonephritis usually occurs in the second or third decade, while malignant hypertension develops in the fourth decade. This fact

16 Michel, J. *Lehrbuch der Augenheilkunde*, Wiesbaden, J. F. Bergmann, 1884.

was pointed out by Fahr and by Ellis and Marrack¹⁷ Further evidence is also present that vascular changes may occur in the apparently normal person and that other vascular diseases are prone to develop in the fifth decade. Brown¹⁸ has pointed out that distinct changes in the capillaries of the nail-folds may occur in normal persons between the ages of 40 and 50 and that thrombo-angitis obliterans occurs most frequently between the ages of 30 and 50

One of the earliest microscopic studies of this condition was that of Gull and Sutton¹⁹ in 1872 They described an arteriocapillary fibrosis which they thought was allied to senile alteration They also pointed out the diffuseness of the vascular lesion and demonstrated a similar thickening in the vessels of the subarachnoid space and in the kidneys Their idea of the capillary involvement has not been universally substantiated but the diffuseness of the lesion of the arterioles is even more extensive than they described Demonstrable morphologic changes in actively functioning capillaries of the nail-folds have been shown to be infrequent This is in harmony with the absence of general involvement of the capillaries in the tissues examined histologically In 1914 Volhard and Fahr described the condition of "malignant sclerosis" or "bosartig hypertension", this condition is analogous, but usually of a somewhat later stage to that which we are describing under malignant hypertension They stress the thickening of the walls of the arterioles and the smaller arteries of the kidney which leads to ischemia of that organ and subsequent parenchymatous changes They found and emphasized the serious prognostic import of retinitis They considered the pathologic changes in the retina to be due to primary ischemia of the arterioles as they are in the kidney

One outstanding fact in this series of cases is the diffuse change in the arterioles This is visible in the retina during life and in the tissues generally on histologic examination The detailed microscopic changes in the wall of the arteriole include a thickening or hypertrophy of its three anatomic divisions The noticeable thickening of the intima and the hypertrophy of the elastic fibers and media make a distinct picture The almost total absence of signs of degeneration is in con-

17 Ellis A W and Marrack J R An Investigation of Renal Function in Patients with Retinitis and High Blood Pressure, *Lancet* 1 891 1923

18 Brown G E Capillary Observations in Cardiovascular Renal Disease, *Ann Clin Med* 1 69 1922 Brown G E and Allen, E V Thrombo-Angitis Obliterans unpublished data Brown G E, and Roth Grace M Biomicroscopy of the Surface Capillaries in Normal and Pathologic Subjects, *M J Australia* 1 499, 1927

19 Gull W W and Sutton H G On the Pathology of the Morbid State Commonly Called 'Chronic Bright's Disease with Contracted Kidney' *Tr Medico-Chir Soc London* 55 273 1872

trast to the many evidences of degeneration in the arteries in cases of senile arteriosclerosis. This lesion of the arteriole suggests hypertrophy which, if steadily progressive, would ultimately lead to occlusion of the lumen of the arteriole. Such occlusions are sometimes found. This is strong evidence in favor of the ischemia hypothesis of Volhard, which offers a logical explanation for the diffuse parenchymatous lesions found in this syndrome.

The association of sustained marked hypertension with diffuse change in the arterioles raises the question whether hypertension or the lesion of the arteriole is primary. So much evidence of hypertrophy in the wall of the arteriole suggests hypertrophy in the face of excessive strain. This interpretation would mean that the change in the arteriole is secondary to the hypertension. If on the other hand the diffuse lesion of the arteriole is primary, sustained hypertension might result on account of increased peripheral resistance. Our experience would lead us to consider the hypertension primary but further study in the early stages of the disease will be necessary to decide the question.

There have been several contributions in which an endeavor has been made to find the primary cause of the hypertension. Bordley and Baker²⁰ attempted to explain it on the grounds of sclerosis of the arterioles of the medulla oblongata, their work being based on some experimental results of Anrep and Starling,²¹ who demonstrated certain definite changes in the general blood pressure that were due to alterations in the blood pressure in the vessels to the medulla. Our histologic studies have not shown more marked changes in the arterioles in the medulla than elsewhere in the brain. Numerous contributions on benign or essential hypertension have been made, including the works of Huchard,²² Allbutt, Janeway, Shaw²³ and Fishberg²⁴ but in general, no serious attempt has been made to distinguish the malignant from the benign type.

The hypertrophied state of the arterioles suggests that the normal effect of vasoconstriction has been aggravated, generalized and made more or less permanent. Whether this phenomenon is due to stimulation of the endings of the sympathetic nerves by pressor substances in

20 Bordley, J, and Baker, B M. Consideration of Arteriosclerosis of the Cerebral Vessels and Pathogenesis of Hypertension, Preliminary Report Bull Johns Hopkins Hosp **38** 320 1926

21 Anrep, G V, and Starling, E H. Central and Reflex Regulation of the Circulation, Proc Roy Soc Med **97** series B, 463, 1925. Starling, E H. The Physiological Factors of Hyperpiesia, Brit M J **2** 1163, 1925

22 Huchard, H. L'arterio-sclerose Presse méd **61** 769, 1909

23 Shaw, H B. Hyperpiesia and Hyperpiesis (Hypertension) London, Frowde, Hodder and Stoughton 1922, p 191

24 Fishberg, A M. Anatomic Findings in Essential Hypertension, Arch Int Med **35** 650 (May) 1925

the circulating blood, to the direct effect of such substances on the musculature of the artery or to some more general disturbance of the sympathetic nervous system is a problem that not only is difficult of solution, but that also is of general importance in the etiology of hypertensive vascular disease

SUMMARY

In cases of sustained high blood pressure and diffuse change in the arterioles, the course of the disease is usually rapidly fatal. The terminal clinical picture suggests simultaneous rapid functional failure of the brain, heart and kidneys. This hypertension syndrome can often be distinguished from benign hypertension and chronic glomerulonephritis. The chief points of distinction from the latter are the age incidence, the characteristic retinal picture, the absence of anemia, and the frequent adequacy of renal excretion. The characteristic histologic observation is diffuse general hypertrophy of the arterioles.

EXPLANATION OF TABLES

Tables 1 and 2 contain the history and the physical and laboratory observations in each case, in tabulated form, and the gross and microscopic pathologic observations in seven cases are given in table 7.

PATHOLOGIC DATA

CASE 1 (case 66 table 7)—Edema (graded 2) was present in the lower extremities and to a lesser degree (graded 1) in the upper extremities, the peritoneal and pleural cavities were free from gross change but the pericardial cavity contained 50 cc of clear straw-colored fluid. The heart weighed 838 Gm, the cavity of the left ventricle was small, and antemortem thrombus was present in the right auricular appendix. Several depressed whitish fibrotic areas were present in the wall of the left ventricle each measuring 1 cm in diameter. The walls of both ventricles were definitely hypertrophied, the left being 2.5 cm and the right 1.3 cm thick. Well marked arteriosclerosis (graded 3) and thickening of the walls of the coronary arteries were present, but the lumina were patent throughout. Slight edema was present in the right lung but the left did not show a gross lesion. The spleen weighed 261 Gm and the liver, 1,735 Gm, chronic passive congestion was present in both. Definite edema (graded 2+) and congestion of the mucosa of the stomach and the small intestine were present.

The left kidney weighed 160 Gm and the right, 142 Gm. The surface of the left kidney was uniformly granular, with many minute bleeding points. On section the cortical markings were indistinct, and the line of demarcation between the medulla and cortex was irregular and indistinct. On the surface of the right kidney were several prominent cortical scars, the largest of which was 1 cm in diameter. The pelvis was dilated (graded 2+) and many sub-epithelial punctate areas of hemorrhage were present. Otherwise, the right kidney resembled the left.

25 The estimated normal weight of the heart for a female of this age, height and weight was 350 Gm.

Arteriosclerosis of the aorta (graded 3) was present, with extensive ulceration of the descending thoracic aorta and calcification of the abdominal portion. The ostia of the celiac and superior mesenteric arteries were partially occluded.

The brain showed atrophy (graded 2) of the convolutions with widening of the sulci and increase in the amount of the cerebrospinal fluid in the subarachnoid spaces. Arteriosclerosis (graded 3) of the vessels in the circle of Willis and of their branches was present. After fixation, the brain was cut by coronal sections at 1 cm intervals. Fresh hemorrhage (a mass 2 cm in diameter) was evident at the level of the postcentral gyrus near the corpus callosum in the corona radiata. There were also many small areas of softening in the midbrain in the region of the medial lemniscus and pons. These areas were rust-colored and diffuse. With a hand lens, the smaller vessels in this portion of the brain were seen to be prominent, having apparently thickened walls and narrowed lumina, multiple minute areas of softening were scattered diffusely throughout, especially in the nuclei of the cerebellum.

Microscopically, changes were noted in the kidneys, especially in their smaller arteries and arterioles. The arterial lumina were diminished, and the walls were hypertrophied or thickened. This thickening was of a peculiar nature: there was evidence of hyperplasia of the intima and accompanying this were hypertrophy and splitting up of the internal elastic lamina, as is usually seen in arteriosclerotic changes. However, hypertrophy of the muscular tissue of the media as well as an increase of the fibrous tissue in and around the adventitia was also evident. In the arterioles there was disproportion of the normal relationship between the thickness of the walls and the lumina of the vessels, the lumen in many vessels being almost completely, or wholly, obliterated. A varying degree of perivascular fibrosis occurred. Most of the capillaries appeared normal, with only occasionally slight hyperplasia of the endothelium or fibrosis around them. The capillary tufts of the glomeruli showed an increase in the number of nuclei, while the tufts in some places were adherent to each other, thus causing a lobulated appearance in many instances. Besides these evidences of vascular disease in the kidneys, other changes were present throughout the parenchyma. Some glomeruli showed changes, being completely hyalinized, others were only partly hyalinized, but many were normal. These changes were different from the crescent formation and the other changes characteristic of glomerulonephritis. The tubules were also affected to a lesser degree. In some places they were irregularly dilated, with flattening of the epithelium, and the lumen contained hyaline casts or cell debris, in other places, they were collapsed and obliterated. Throughout the entire kidney, there was marked interstitial fibrosis in the midst of which was abundant evidence of destroyed tubular epithelium. There were also some discrete masses of lymphocytes. A scharlach R stain revealed the presence of a small amount of fat in the epithelium of some tubules and in the intima of a few arterioles, but not in the glomeruli.

The arteries in the spleen showed marked thickening of the media and adventitia. The internal elastic lamina was hypertrophied and in many places split up, and a minor degree of hyperplasia of the intima was present. The external elastic lamina was also hypertrophied and split up. The arterioles showed slight adventitial fibrosis and the internal elastic lamina was hypertrophied and split, as in the arteries, the external elastic lamina was hypertrophied and divided into many fine layers of elastic tissue. Between these two elastic laminae, the media appeared to be composed of fibrinohyalinoid tissue rather than of true muscle tissue. Intimal proliferation could occasionally be observed, and some medial hyperplasia was seen. Little reticular fibrosis was present.

Throughout the parenchyma of the pancreas there was mild interstitial fibrosis, but the islands apparently were unaffected. The arteries and arterioles showed changes similar to those seen in the kidneys, but less marked. Certain small vessels, as in the kidney, showed a change with hypertrophy and splitting up of the internal elastic lamina and fibrosis of the adventitia. Occasionally slight thickening could be seen in certain capillaries, but the majority of these vessels were free from any appreciable change.

The arteries in the liver were considerably thickened and showed changes similar in degree to those in the pancreas, the arterioles were affected to a like extent, the media manifested muscular hypertrophy and an excessive amount of fibrous tissue was present in the adventitia. The elastic tissue was hypertrophied, and the intima was hyperplastic. The sinusoids were dilated but fibrosis was absent, with the exception of that already mentioned.

The vasa vasorum of the aorta had definitely thickened walls, the elastic tissue was slightly hypertrophied, the intima was increased in thickness, and excess fat was present in this coat. The coronary arteries showed slight arteriosclerotic changes similar to those seen in patients of this age, but the arterioles of the myocardium had thickened walls and narrowed lumina, although to a much less degree than those in the kidneys. Many of the individual fibrils of the myocardium were hypertrophied to several times their normal size but were free from fat, diffuse fibrosis was seen throughout the muscular tissue, which in places was completely replaced by dense bands of fibrous tissue. The capillary walls were not fibrosed or thickened.

The arteries and arterioles of the lung were slightly involved in this general change but less than in most other organs and, as elsewhere, the capillaries appeared to be almost free. A considerable number of the so-called heart failure cells were present in some of the alveoli. Few arterioles were seen in the suprarenals, but the ones that were present had thickened walls and narrowed lumina. Several were obstructed by the presence of antemortem thrombi, but showed early canalization.

The vessels in the brain were less affected than those of other organs. Those in the subarachnoid space were undoubtedly thickened but to a much less degree than those of the kidneys. The ratio of vessel wall to lumen in the arteries was almost normal. In the arterioles the walls were slightly thickened, but splitting of the internal elastic lamina was not observed. The intima was hyperplastic, the media did not show hypertrophy, and there was slight perivascular fibrosis and thickening of the adventitia. In the brain tissue proper, the same changes existed, except that occasionally an arteriole was encountered with definite general thickening of its walls. The smallest arterioles showed slight intimal hyperplasia. It was difficult to determine whether these small vessels were arterioles or capillaries. The capillaries showed a slight increase in the number of nuclei in their walls, but other appreciable change could not be distinguished. Vessels from different areas of the brain were examined (fourth ventricle, midbrain, basal nuclei and various places in the cortex), and these observations were consistent throughout. Areas of hemorrhage and numerous small areas of softening contained considerable amounts of blood pigment with numerous "scavenger" cells, and the vessels supplying some of these areas seemed to be partly occluded by proliferation.

In the eye the choroidal vessels were definitely thickened, and the lumina was narrowed sometimes even as much as in the renal vessels. Proliferation of the intima was present. The media was hypertrophied, and perivascular fibrosis was present. Occasionally an arteriole was encountered in which the lumen was completely occluded by the intimal proliferation (fig 14). In the retinal

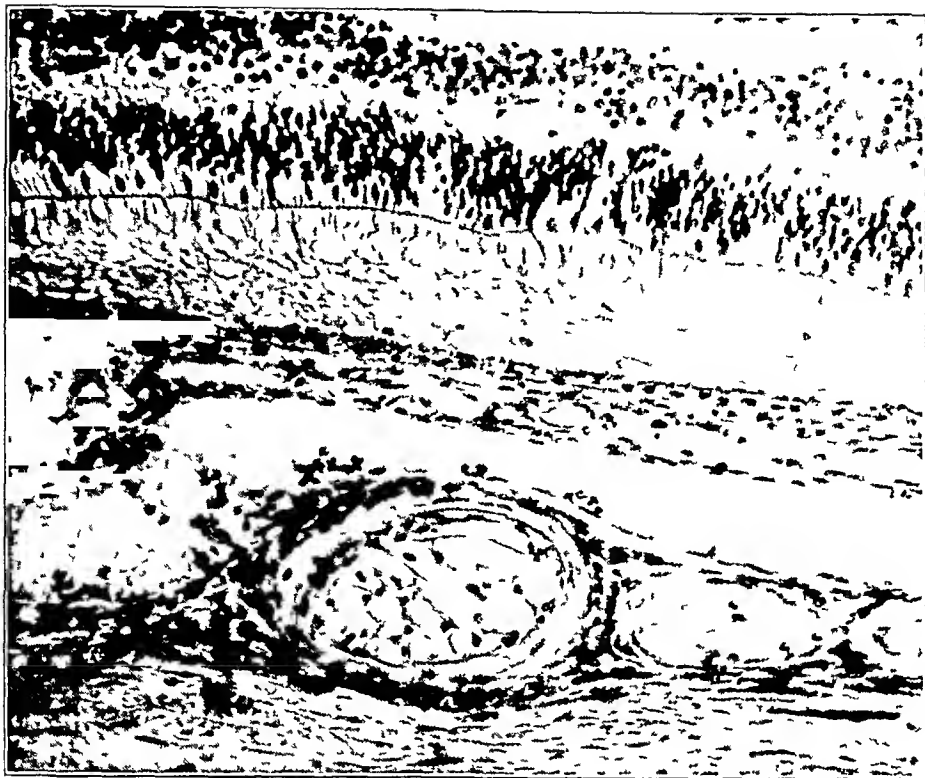


Fig 14—Complete occlusion of one of the choroidal arterioles and a proliferation of the retinal pigment epithelium between the choroid and the retina
Hematoxylin and eosin, $\times 175$



Fig 15—Collection of cytooid bodies in the layer of nerve fibers of the retina
Hematoxylin and eosin, $\times 150$

arteries the thickening was not, as a rule, due to excessive intimal changes but to gliosis around the vessel combined with slight medial hypertrophy. The internal elastic lamina was hypertrophied. The arterioles had thickened walls, due apparently to a medial rather than to an intimal change. The adventitia was surrounded by an excessive number of delicate fibrils which streamed off into the surrounding tissue. As in the brain, the capillaries showed a slight increase in the number of nuclei distributed along their walls. Surrounding the optic disk was a mass of homogeneous eosin-staining substance²⁶ between the retina and the choroid. Small collections of a similar substance were seen at various places in the retina, they were most numerous in the internuclear layer, but also were present in the inner molecular layer and even in the layer of ganglion cells. Large fresh hemorrhages were abundant, involving the layer

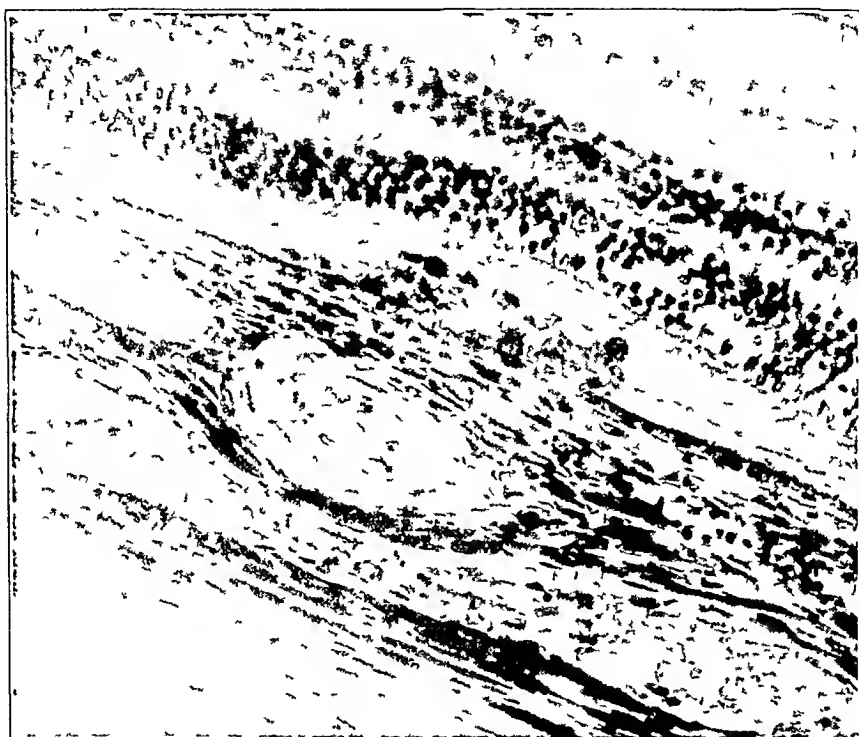


Fig 16—Small choroidal artery filled with large clear cells, probably due to proliferation and degeneration of the lining endothelial cells. Slight exudate between retina and choroid. Hematoxylin and eosin, $\times 150$

of nerve fibers, the layer of ganglion cells and the inner molecular layer, but they were also observed to penetrate all the layers of the retina, while minute hemorrhages were abundant in the internuclear layer and not so common elsewhere. There was evidence of glial proliferation throughout the retina, this was most marked in the region of the optic disk, where definite thickening was noted with an excessive number of glial cells as well as signs of edema, evidenced by widening of the spaces between the fibrils. Occasionally large masses of "cystoid bodies" (fig 15) were encountered. In the internuclear layer, large

26 Older authors on this subject have used the word "exudate" to designate this substance. In view of the uncertainty in regard to its true nature or origin, we have been impelled to avoid this term in the histologic descriptions.

"foamy" cells were found (figs 7 and 11). In some spots, they were present around the eosin-staining substances already mentioned, in others, they seemed to be alone. Some of the choroidal arteries (fig 16) contained a type of cell similar to those just noted in the retina, but it is impossible to explain the presence of such cells within the lumina of arteries, and in all probability the foamy cells within the arteries have a different origin. They were probably proliferated, swollen and degenerating endothelial cells, and as a matter of fact various stages of the process of their formation were present in different vessels. It seems unlikely that these cells were the result of postmortem changes, although this source of origin has to be considered.

CASE 2 (case 80, table 7)—Emaciation (graded 2) was present, but edema and excess of fluid did not occur in any of the cavities of the body. The heart weighed 496 Gm,²⁷ the cavities were not dilated, but there was definite thickening of the ventricular walls (left, 2 cm and right, 0.5 cm). The coronaries showed arteriosclerosis (graded 3), but they were not notably narrowed. Early bilateral embolic pneumonia was present in both lungs. The spleen, liver, pancreas, suprarenals and stomach did not show noteworthy lesions. In the cecum and ascending colon, acute ulceration apparently limited to the mucosa was present. The left kidney weighed 100 Gm and the right, 106 Gm. After the capsules were stripped off, the kidneys had a granular surface with scars, some of which measured 4 mm in diameter, and a few cysts 7 mm in diameter. On section, the cortex was thin and the markings indistinct and irregular, while there was an increase in peripelvic fat. The right kidney contained a fresh infarct. The brain showed slight atrophy of the frontal convolutions, and the vessels of the circle of Willis were sclerosed (graded 3), the basilar arteries were dilated and also sclerosed (graded 3). On section of the brain, numerous small areas of hemorrhage, the largest of which was 1.5 cm in diameter, were found in many places. There were also numerous areas of softening, some having formed cavities or cysts, these areas were smaller than those showing hemorrhage, the largest being 8 mm in diameter.

On microscopic examination, the arteries of the kidney had definitely thickened walls due partly to hyperplasia of the intima, with hypertrophy and splitting up of the internal elastic lamina, and partly to hypertrophy of the medial muscular layer. There was also an increased amount of connective tissue in and around the adventitia. Many of the arterioles were almost completely obliterated, and some were occluded by intimal proliferation and definite hypertrophy of the media. In others the occlusion was by no means complete, but in all, thickening of the walls was marked. The capillaries showed little appreciable change, except those of the glomerular tufts, in which apparent cellular proliferation was present. Many glomeruli were more or less completely hyalinized, while in others the tuft was lobulated and there were some adhesions to the capsule. The capsule in some was thickened by an excess of fibrous tissue. Throughout the parenchyma interstitial fibrosis occurred. Some of the tubules were dilated to form small cysts. Here and there, small collections of lymphocytes were encountered.

The walls of the arteries in the spleen were much thicker than normal, and the intima was hyperplastic, while the internal elastic lamina was greatly hypertrophied and split up. The media was also excessively thickened by a fibrous hyaline type of tissue. Some of the arterioles were almost occluded by

27 The estimated normal weight of the heart for a patient of this age, height and weight was 200 Gm.

concentric hyperplasia of the intimal cells, and some were actually obstructed. The walls of some of these arterioles were hyalinized. Throughout the splenic pulp, moderate reticular fibrosis was present.

In the pancreas and liver there was definite thickening of the walls of the arterioles but much less in the walls of the arteries.

In the small intestine, the arteries and arterioles of the submucous and muscular coats showed thickening of their walls. In the cecum this thickening was more marked than in the small intestine and its submucosa was thick and edematous, the mucosa was absent in many places, and large numbers of polymorphonuclear leukocytes were present, as well as large masses of necrotic tissue.

There was a mild degree of sclerosis in the arteries and arterioles of the subarachnoid space, not comparable in any degree with those of the kidney or any other organ examined. In the brain parenchyma proper, the walls of most of the arterioles were definitely thickened, due mainly to intimal proliferation. Around some of the areas of softening, the arterioles were more or less obstructed by intimal proliferation. In some of these softened areas, large masses of blood pigment, which did not react to an iron stain, were present. With the blood pigment, large "scavenger" cells and edema were present.

In the eye, the lumina of the choroidal vessels were narrowed and their walls were thickened, this change was mainly the result of hyperplasia of the intima, but the media was also hypertrophied. Some of the arteries and arterioles were apparently completely occluded. In the lumina of certain arteries (fig 16), large clear cells were abundant, intermingled with endothelial and connective tissue cells, one such artery showed canalization. In the retina the arterial change was much less marked than in the choroid, and the thickening was due mainly to hypertrophy of the media. The intima was only slightly changed. Numerous small areas of hemorrhage and masses of homogeneous, eosin-staining substance were present in the internuclear layer. Evidence of recent hemorrhage was occasionally seen in the layer of nerve fibers. Around some of these eosin-staining masses, large "foamy" cells might be seen. One large mass was present between the retina and the choroid at the entrance of one of the short posterior ciliary arteries. Here and there, proliferation of the retinal pigment epithelium also was present (fig 14).

CASE 3 (case 81, table 7)—Slight edema (graded 1) of the ankles was present. ascites was not present, but the left pleural cavity contained 1,000 cc and the right, 50 cc of clear straw-colored fluid, the pericardial cavity contained 150 cc of similar fluid. The heart was greatly hypertrophied, weighing 870 Gm³ but it was not dilated, the left ventricular wall measured 2.2 cm and the right, 0.6 cm. Slight myocardial fibrosis and only slight sclerosis (graded 1) of the coronary arteries were present. The spleen weighed 215 Gm and the liver, 2,116 Gm. The colon contained multiple areas of petechial hemorrhage. The left kidney weighed 165 Gm, and on removal of the capsule the surface was coarsely granular and congested. On section, the cortex appeared narrow, but a few glomeruli could be seen grossly while the medullary markings were indistinct and irregular. There was a definite increase in the peripelvic fat. The right kidney was not examined. Arteriosclerosis (graded 2) of the aorta was noted. In the circle of Willis arteriosclerosis was pronounced (graded 3), and throughout the brain multiple small areas of softening were noted, but

28 The estimated normal weight of the heart of a patient of this age, height and weight was 310 Gm.

fresh hemorrhage was not evident. These softened areas were most abundant in the left lenticular nucleus and also near the left optic radiations, but they were also present throughout the cerebrum, they were not so abundant in the cerebellum, and none were noted in the pons or medulla oblongata. The posterior half of the right eye showed a considerable number of hemorrhagic areas, grayish exudates and apparent edema of the tissue around the optic disk.

Microscopically, the vessels of the kidneys showed profound change. In the arteries all the three coats of the vessels were involved, particularly the intima and media. The internal elastic lamina was also hypertrophied and thickened. In some vessels in the intima and between the intima and media, there was a considerable amount of mucoid material. The walls of the arterioles were thickened, and the lumina were obstructed more uniformly and completely than the arteries, this partial occlusion was mainly due to intimal hyperplasia, although some hypertrophy was also present in the media, and there was considerable fibrosis around the vessels. The capillaries appeared normal, except in the glomeruli. Throughout the kidney marked interstitial fibrosis was present, and many of the tubules were dilated and the epithelium flattened. In many of the lumina were homogeneous, colloid-like casts. In the midst of the fibrous tissue the remnants of numerous collapsed and shrunken tubules were noticed. Some glomeruli were hyalinized, a few had thickened capsules but the remainder seemed to be hypertrophied, there was also an increase in the number of nuclei in the tuft.

Mild reticular fibrosis was present throughout the spleen, and the walls of the vessels were thickened but not to such an extent as in the kidney. Intimal hyperplasia was seen, and the tissue immediately outside the intima was of a hyaline-like consistency, in the adventitia, there was moderate fibrosis.

Partial fatty replacement (graded 2) of the pancreatic pulp was seen. The walls of the arteries and arterioles were considerably thickened, while the capillaries were free from any appreciable change.

The arteries of the liver showed well marked hypertrophy of the media and hyperplasia of the intima. All the coats of the walls of the arterioles were thickened, but less so in the adventitia.

In the heart, muscle fibers were hypertrophic and were partially replaced by connective tissue. The media in its arteries was hypertrophied and the adventitia also, to a slight extent, while the intima showed only slight hyperplastic change. The arterioles were moderately affected, but the capillaries were free from any noticeable change.

In the aorta there was some calcification in the intima and media, but the most profound change was in the vasa vasorum, which in many places were almost occluded by the excessive hypertrophy of the media and hyperplasia of the intima. Around some of these vasa vasorum, there were collections of lymphocytes. The arterioles of the skeletal muscles showed hyperplasia of the intima as well as definite hypertrophy of the media and hypertrophy and splitting up of the internal elastic lamina.

The thyroid did not show signs of hyperactivity.

The intima in the basilar artery was thick, and areas of softening were present, while the media showed only mild hypertrophy. The lumina of the choroidal arteries and arterioles were almost obliterated, partly by hypertrophy of the media but more particularly by hyperplasia of the intimal endothelium. The internal elastic lamina was also hypertrophic and split. In the retina the vessels were like the vessels of the subarachnoid, and there was hypertrophy of the media but little intimal change. Some hypertrophy of the internal elastic

lamina also was present. The capillaries seemed to be free from fibrosis. Areas of hemorrhage were present but were not numerous. Evidence of larger recent hemorrhages was noted in the layers of nerve fibers and ganglion cells, while smaller and older hemorrhagic areas were present in the internuclear layer. Small masses of eosinophilic substance were also present in this layer, while a large mass was present in the layers of nerve fibers and ganglion cells.

The arteries and arterioles of the subarachnoid space showed hypertrophy of the medial coat but little change could be found in the intima or adventitia. In the brain parenchyma proper, the vascular changes found in the arteries were similar to those of the subarachnoid space. The arterioles of the brain tissue proper, on the other hand, showed proliferation of the intima and also hypertrophy of the media. The areas of softening were characterized by blood pigment, "scavenger cells," edema and necrosis.

CASE 4 (case 37, table 7).—Edema (graded 1) was present in the lower extremities, but other abnormal collections of fluid were not found in the upper extremities or cavities of the body. The heart weighed 400 Gm,²⁹ the left ventricular wall was hypertrophied. A coronary sclerosis (graded 2) was present. In the right lung, there were bronchitis and early bronchopneumonia. Chronic passive congestion was found in the liver, but the spleen, pancreas, suprarenals and gastro-intestinal tract were without gross lesion. The kidneys weighed 135 Gm each. Stripping the capsule revealed a fine granular surface. On section, the cut surface showed some pale areas. Arteriosclerosis of the aorta was graded 1+. Blood was diffusely present in the subarachnoid space, also in both lateral ventricles, especially in the left, this ventricular blood had evidently come from hemorrhage in the region of the left internal capsule, with destruction of tissue of the brain. Small areas of rust-colored softening, the largest of which was in the right thalamus, were present.

Microscopically, the arteries in the kidneys showed thickening of their walls, in the intima and the inner portion of the media, hyalinization was seen. The walls of the arterioles were thickened, and there was well marked intimal proliferation and hypertrophy of the media, so that the lumina in many places were almost occluded, in others, the lumen was obstructed and the walls hyalinized. Some glomeruli appeared to be hypertrophied, with lobulation of their tufts and partial hyalinization. In others, there was an increase in the number of nuclei in the capillaries while some capsules were thickened. An occasional cyst could be seen, but most of the tubules were normal. A few hyaline casts were seen in the loops of Henle. Interstitial fibrosis was also evident and small collections of lymphocytes were seen.

Thickening of the walls of the coronary arteries was seen, but the arterioles showed a more advanced change. The myocardial fibers were slightly hypertrophied.

In the pancreas there was marked hyalinization of the islands of Langerhans, so that few normal islands remained. The arterioles of the pancreas, liver, spleen and suprarenals showed thickening and partial obstruction.

In the brain the walls of the arterioles showed hypertrophy of the media, which in some places was split and contained large fat cells, the intima was hyperplastic. In some of the perivascular spaces, collections of "scavenger" cells were present. In many of the arterioles the media was hypertrophied and the intima was hyperplastic so that the lumen appeared almost occluded. This

²⁹ The estimated normal weight of the heart of a person of this age height and weight was 265 Gm.

change was present in all the sections examined. The capillaries did not show any appreciable change. Areas of softening were abundant and many ganglion cells showed various stages of chromatolysis.

CASE 5 (case 32 table 7)—The body was obese (graded 3) and edema (graded 2) of the lower extremities was found. Ascites and hydrothorax on the right (1000 cc) were present but an estimation of the fluid in the pericardial cavity is not on record. The heart weighed 870 Gm³⁰ all the cavities were dilated and hypertrophied; the left ventricle was 2 cm thick and the right, 0.6 cm thick. Fibrosis (graded 3) of the myocardium was a marked feature on gross examination and there seemed to be incompetence of the mitral valve, owing to stretching of the ring which measured 11 cm. Mild sclerosis (graded 1) of the coronaries was present. The spleen and liver were larger than normal. Gross lesions were not observed in the gastro-intestinal tract or the pancreas. The left kidney weighed 190 Gm and the surface was roughly granular after the capsule had been stripped. On section the cortex was thin and the markings were indistinct. The right kidney was similar to the left.

Microscopically the arteries of the kidneys showed hypertrophy of the media, the intima was hyperplastic and there was hypertrophy and splitting up of the internal elastic lamina. An excessive amount of fibrous tissue was present in the adventitia and also immediately near it. The arterioles were more involved than the arteries; the media was hypertrophic but the hyperplastic change of the intima was the outstanding feature in many vessels; in others it was the medial change. In some arterioles these processes had advanced to the point of complete occlusion of the lumen. Many glomeruli were completely hyalinized while others were only partly destroyed. In a large number the capsules were thickened. Few tubules were dilated but many were completely collapsed, shrunken or disintegrated.

Slight central necrosis was present in the liver and in this organ the walls of the arteries and arterioles were thickened.

In the heart the media of the coronary arteries was hypertrophied; the intima did not show appreciable change but there was increased fibrosis in and around the adventitia. Certain arterioles were almost occluded but others were patent; around the former there was advanced fibrosis. Some fibers were hypertrophied and many were seen to contain minute droplets of fat especially around the nuclei but also elsewhere within the fiber.

CASE 6 (case 26 table 7)—Edema was present over the forearms and backs of the hands (graded 2) and ankles (graded 1) but there was not an excess of fluid in any of the cavities of the body. The heart weighed 715 Gm³¹ and showed hypertrophy of the ventricular walls the left being 2 cm thick and the right, 0.6 cm thick. The myocardium did not show gross fibrosis. The coronaries were sclerosed (graded 2). Slight edema and congestion were present at the base of both lungs. The spleen, liver, pancreas, suprarenals and gastro-intestinal tract did not present notable lesions. The kidneys weighed 97 Gm each and the surfaces were granular with many small whitish nodules scattered over the surface as well as a few small cysts containing clear yellowish fluid. On section the cortices were thinner than normal being 5 mm thick and

30 The estimated normal weight of the heart of a person of this age, height and weight was 370 Gm.

31 The estimated normal weight of the heart of a person of this age, height and weight was 270 Gm.

the medullary markings were irregular but fairly distinct. Arteriosclerosis of the aorta was graded 2 and a few discrete areas of calcification were present in the abdominal portion. Histologically, the arteries of the kidneys showed marked change in the normal ratio of blood vessel wall to lumen, the latter was constricted and the former thickened, due to hypertrophy of the media and internal elastic lamina, which was split and contained the hyperplastic intima within its meshes. In the adventitia, there was an increased amount of connective tissue which was also present around the vessel. The arterioles showed changes similar in degree. The capillaries were free from any change in their walls, except in the glomerular tufts. Some glomeruli were hyalinized, but the majority appeared to be increased in size, in some there appeared to be an increase in the number of nuclei in the capillaries of the tufts. Many tubules were dilated and contained hyaline or epithelial casts. Interstitial fibrosis was present, while collections of lymphocytes were rare. The walls of the coronary vessels were not thickened, but the myocardial fibers were definitely hypertrophied. In the pancreas, liver, spleen and lungs there were hypertrophic vascular lesions involving the arteries and arterioles but again the capillaries seemed to be free.

CASE 7 (case 45 table 7) —The necropsy in this case was performed elsewhere, and we received only portions of the kidneys for microscopic examination. Sclerosis was present in most of the smaller arteries and arterioles, while others were less affected. Some glomeruli were completely hyalinized, others were only partially hyalinized, a small portion or even half of a glomerulus being destroyed in this way. Most of the glomeruli showed apparent hypertrophy and an increase in the number of nuclei in the capillary tufts, but in a few the capsule was thick. Interstitial fibrosis was present throughout the kidney. In certain areas, some of the tubules were dilated and filled with hyaline-like casts, but in other areas only a few epithelial cells remained in the increased fibrous tissue to indicate the presence of destroyed tubules. In a considerable number of tubules, the epithelium was well preserved.

BACTERIOPHAGY IN URINARY INFECTIONS FOLLOWING THE ADMINISTRATION OF THE BACTERIOPHAGE THERAPEUTICALLY*

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It has been shown that sewage filtrate contains lytic principle of marked activity for most of the gram-negative bacilli found in cases of urinary infections¹ Of seventy-five consecutive cases of urinary infections which I have studied up to the present time, sewage filtrate has lysed 90 per cent of the strains of bacilli isolated from the catheterized specimens of urine The activity of the sewage filtrate is marked, either in the first passage or after only one or two passages A complete report of this phase of the subject will be made after the series has been extended

Because of the ease with which the lytic principle could be obtained from sewage filtrate for these organisms, and the fact that in the past the chief obstacle to the use of the bacteriophage in urinary infections has been the lack of potent bacteriophage to many of the causative bacilli, the situation appeared hopeful for the treatment of the patients with sewage filtrate A small number of patients, twelve in all, have been treated recently, and the processes of bacteriophagy have been followed through frequent cultures of urine and examinations of urine filtrates Certain observations have been made which have influenced the mode of treatment, and which throw some light on bacteriophagy in the human body There is a striking paucity of such observations in the literature, and even the few reported are in conflict, so that there is reason for presenting in some detail such a small number of cases at this time The clinical and therapeutic phases will not be given here, except to say that the cases were chronic, and in most instances the patients had been treated by other methods

The chief observations that have been reported on the fate of injected bacteriophage have been made in two types of studies (1) studies of the viscera at various intervals when bacteriophage was injected into normal, uninfected animals, (2) studies of animals after the simultaneous administration of bacteriophage and susceptible organisms

Experiments of the former sort are summarized in d'Herelle's book, "The Bacteriophage and Its Behavior"² There is general agreement

* From the Baylor Hospital Laboratory

1 Cowie D M Observations on the Bacteriophage, Ann Clin Med 5 57 (July) 1926 Caldwell, Janet Sewage Filtrate as a Source of Bacteriophage, J Infect Dis 4 575 (May) 1927

2 D'Herelle, F The Bacteriophage and Its Behavior, Baltimore, Williams & Wilkins Company, 1926, p 381

that the bacteriophage does not persist in normal organs, it disappears from most of them as early as three hours after injections, and from all of them after twenty-four hours

Arnold and Weiss³ have used the second method in testing the efficiency of their protein-free filtrates. In these experiments, they injected lethal doses of Shiga dysentery or typhoid bacilli simultaneously or at short intervals with the bacteriophage. They did not produce experimental disease comparable to the pathologic conditions in man. They believe from their observations that bacteriophage does not increase *in vivo* as *in vitro*, and that, therefore, a large proportion of bacteriophage is necessary (comparable to the proportion which prevents clouding of tubes *in vitro*) to effect cure of lethal doses of *B. typhosus*. The author's experience and that of others in cases of urinary infections in which natural disease exists is at variance with such conclusions.

Schumm and Cooke⁴ have reported the constant recovery of homologous bacteriophage administered in staphylococcus infections of the nasal sinuses. They do not report any diminution in organisms or pus, nor any acquisition of resistance of the culture in association with the bacteriophage. The following observations confirm the fact that the bacteriophage can be recovered from the products of the lesions and is constantly present when cure is not effected, but it has always been possible to demonstrate readily resistance of the culture to the bacteriophage.

The bacteriophage used in treatment was isolated from sewage filtrate in the usual way and was built up on the patient's organism by a few serial passages until it gave maximum or marked lysis. It was always concentrated by adding an entire agar slant suspension to 20 or 25 cc. of the filtrate and incubating until lysis occurred (from eight to eighteen hours). This concentrated filtrate was given by subcutaneous injections and lavage of the bladder, usually daily or every other day for from three to six injections.

DIAGNOSIS OF ORGANISMS TREATED

In classifying the organisms isolated from the catheterized specimens of urine, the usual culture mediums were used: gelatin, Russell's medium, dextrose and lactose broth, litmus milk and citrate agar. *B. coli* was present in pure culture in eight cases, in three cases *B. pyocyaneus*, associated with a streptococcus in two. In one case the

3 Arnold, Lloyd and Weiss, Emil. Prophylactic and Therapeutic Possibilities of the Twort-d'Herelle's Bacteriophage, *J. Lab. & Clin. Med.* **12**: 20 (Oct.) 1926.

4 Schumm, Elsie, and Cooke, Robt. Incidence and Therapeutic Value of Staphylococcus Bacteriophage in Antrum Infections, *J. Infect. Dis.* **39**: 424 (Nov.) 1926.

organism had the culture characteristics of *B. pyocyaneus*, and during treatment it developed a diffuse, pale lavender pigment, therefore it was considered to be an atypical *B. pyocyaneus*.

Dissociation phenomena were present in all the cultures and by the use of the artificial colony method the stage of dissociation as elucidated by Hadley⁵ could be recognized. No difference which correlated with any one stage of the dissociation cycle could be detected in the ease with which these organisms could be lysed by sewage filtrate. This has also been true of the large group of urinary organisms now being studied.

BACTERIOPHAGE IN URINE

Frequency of Native Bacteriophage in Patient's Urine—Before beginning to treat the patient a urine filtrate was obtained. This was

TABLE 1—Results of Examinations of the Urine of Patients Treated with Homologous Bacteriophage

| Serial No. | Diagnosis | Bacteriophage in Urine | | Time of Appearance | Persistence | Urine Culture | Time to Become Sterile | Resistance Developed |
|------------|------------------------|------------------------|-----------------|--------------------|-----------------------------|---------------|------------------------|----------------------|
| | | Before | After | | | | | |
| 13U | B. coli | — | — | | | Sterile | 3 days | — |
| 18U | B. pyocyaneus | — | — | | | Sterile | 27 days | — |
| 34U | B. coli | — | — | | | Sterile | By 10th day | — |
| 74U | B. coli | — | — once | 48 hours | Gone in 48 hours | Sterile | 5 days | — |
| D | B. coli | — | — | 1½ hours | 31 days | Sterile | 36 hours | — |
| 1U | B. pyocyaneus | — | — | Not followed | | — | | — |
| 9U | B. coli | — | — | 3 days | 4 mo | — | | — |
| 17U | B. pyocyaneus | — | — | 3 days | 1 mo | — | | — twice |
| 24U | Atypical B. pyocyaneus | — | — | By 11th day | 1 mo | — | | — |
| | | | suicide culture | | | | | |
| 36U | B. coli | — | — | 25 days | Died | — | | — |
| 64U | B. coli | — | — | 2 hours | 36 hours | — | | — |
| 67U | B. coli | — | — | 6 hours | Treatment was not completed | | | — |

examined for the presence of a bacteriophage by testing through five passages against a stock *B. dysenteriae*, *B. coli* and the patient's own organism. I am convinced that this method does not give the true notion of the frequency of bacteriophage in the urines but it is about as extensive a method as is practical.

Typical bacteriophage phenomena (plaques and lysis) were obtained from the urine filtrates of two patients, both cases in which *B. pyocyaneus* was present. In large series of urines tested⁶ the frequency of native bacteriophage is from 20 to 25 per cent.

Recovery of Bacteriophage Administered—Bacteriophage could be recovered in all urines following treatment except those which became sterile (table 1). Of the latter cases 74U showed the bacteriophage on

5 Hadley, Philip. Microbic Dissociation. J. Infect. Dis. 40:1 (Jan.) 1927.

6 Larkum, N. W. Bacteriophagy in Urinary Infections. J. Bact. 12:203 (Sept.) 1926.

only one examination, but D showed it persistently. D is an exceptional case, it is the only case in which the urine became sterile and in which the bacteriophage was strong and constant in the urine, so that a more detailed account of it is necessary to explain the apparent inconsistency. The patient had a puerperal infection in which a hemolytic *B. coli* was isolated from the blood. Besides pyelitis, colitis was present. The fact that the bacteriophage persisted in the sterile urine is, I believe, evidence that lesions due to this bacterium were still present in the body. The urine of D became sterile in thirty-six hours after beginning treatment, but the urine continued to give maximum lytic action as already stated, so that I was not surprised when a few colonies returned at the end of five days, accompanied by a return of symptoms. The few colonies persisted for weeks, always in the presence of a strong bacteriophage. These colonies always gave typical suicide cultures, that is, they could be cultivated on agar for a few generations, but finally gave ragged growth and then sterile slants, while in broth either they failed to grow or the slightly cloudy cultures cleared early. Thus D illustrates a typical mixed culture of a bacteriophage of maximum virulence and a susceptible bacterium, a condition described in vitro by d'Herelle.

The bacteriophage recovered in the urine was always similar in strength to the one administered but could not always have been demonstrated unless the original culture had been available, for the bacteriophage strains for the heterogeneous colon and allied organisms are specific and limited in their range of activity, and the organisms in contact with them become modified and resistant early.

Time of Appearance of Bacteriophage in Urine—The time of appearance of the bacteriophage in the urine during treatment varied. In some cases it could not be recovered before the third day, while in other cases it appeared in a few hours. To try to determine how early the bacteriophage might appear, three patients were given the first subcutaneous injection from one to three hours before the first lavage of the bladder. The urine was drawn off before the filtrate was instilled into the bladder, cultures were made immediately, and the filtrate was studied. In one of these cases, D, many plaques were present in the agar plate culture one and one-half hours after giving 2 cc subcutaneously, and the urine filtrate was as strong as the concentrated bacteriophage administered.

In a second case, 64U, a similar positive filtrate was obtained two hours after the first injection. In a third case, 67U, the urine obtained in thirty minutes was negative, but when the urine was drawn off six hours later, its filtrate contained the bacteriophage.

Thus it appears that the bacteriophage, when administered subcutaneously, may appear in the urine of infected patients within two

hours. It can be recovered constantly in cases in which the organisms persist but when the urine becomes sterile it is not present or is transitory. This indicates that the decisive action of bacteriophage on the organism occurs in the lesions and when the lytic action is promptly successful the bacteriophage cannot persist. This is consistent with bacteriophage action *in vitro* where its sole medium for growth is the living bacterium. The situation just described was really the opposite of what was expected for it seems at first inconsistent that the presence

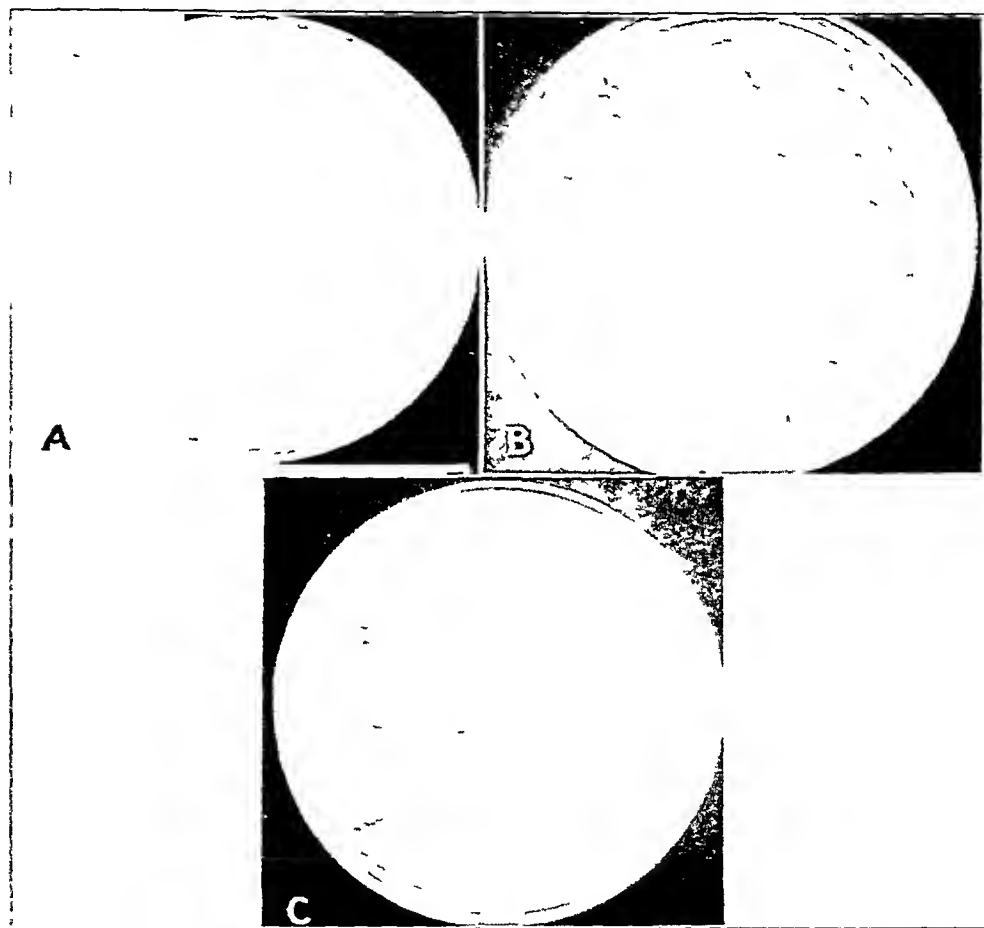


Fig 1—Evidence of lysis in cultures during treatment. A indicates a culture of urine just before treatment was begun a typical normal growth. B (case D) indicates a culture of urine taken one and one-half hours after 2 cc. of bacteriophage was given subcutaneously note the plaques. Thirty-six hours later cultures were sterile. C (case 74U) shows a culture taken after forty-eight hours of treatment. Sterile cultures were obtained after the fifth day.

of the bacteriophage in the urine is unfavorable for the ultimate cure of the patient but on closer thought it is really what should happen if the action of the bacteriophage is similar *in vivo* to results in the test tube. In the latter the action of the bacteriophage if it prevents the development of secondary cultures must be violent and early any action less than this can produce mixed cultures of bacteriophage and

organisms representing all degrees and stages of equilibrium, some of which persist through many transfers. That this is what happens in the body and explains the simultaneous presence of the bacteriophage and the organism in the urine, will be brought out in the following description of the changes in cultures during the administration of the bacteriophage.

Persistence of Bacteriophage in Patient's Urine—When the organisms persisted in the urine, the bacteriophage remained for some time and in certain cases which were followed could be demonstrated for months after treatment was discontinued. Naturally, the data here is incomplete, as the work is too recent to have allowed a long period of observation. In three instances, twice in 17U and once in 24U, the bacteriophage disappeared after about one month, and the organism was found to be reverting to its original cultural characteristics.

The persistence of the bacteriophage in the urine for such periods can scarcely be interpreted in any other way than as evidence of its increase in the body when natural lesions and organisms are present.

EFFECT OF BACTERIOPHAGE ON ORGANISM

One of the most striking results of administration of bacteriophage is the effect produced on the organism. The modification in growth or pigment characteristics were so striking that a systematic study of the cultures during treatment was undertaken early. Observations were made on the cultural and growth characteristics and on the susceptibility to the bacteriophage administered and to sewage filtrate.

The artificial colony method is an excellent way to note size, shape, density, thickness, pigment production and dissociation phenomena of a culture. Freshly poured and hardened agar plates are inoculated by stabbing the center with a straight platinum wire which has previously been carried over a twenty-four hour agar slant culture. The central colonies are measured and observed at regular intervals for any length of time, usually ten days.

The results of these studies have been summarized in table 2. In all cases in which the urine was not sterilized, and in some of the latter cases before sterilization, the organism was modified. The change occurred promptly, in from fifty-six hours to eleven days, and usually persisted for some weeks, with reversion after the bacteriophage disappeared from the urine. The changes did not affect the cultural characteristics of the organism in any case, the diagnosis was, therefore, the same. The organism as modified was always resistant to the bacteriophage administered, but could be lysed by sewage filtrate with but one exception. These tests were carried out for one passage only, and the new culture was not studied in poured plates to determine its various

constituents of sensitive and resistant colonies. Doubtless the modified cultures represent such composite cultures, or the bacteriophage could not exist in its presence.

As to modification of growth characteristics, these were not consistent either in degree or in type of change produced. No change could be noted in two instances, 9U and 67U, resistance was the only sign of modification in these cultures. In this connection 9U proved to be an unusual organism, for it always developed early and perfect secondary cultures to any bacteriophage found for it so that, although lysis was

TABLE 2—*Modification of Urinary Cultures During Treatment with Homologous Bacteriophage*

| Serial No. | Original Characters | Modified Characters | Modified Culture Tested with | | Time for Modification | Tendency to Reversion |
|------------|---------------------|-----------------------|------------------------------|-----------------|-----------------------|--|
| | | | Treatment Bacteriophage | Sewage Filtrate | | |
| 1U | Green pyocyanineus | Gave amber colonies | R | Lysed | 3 days | |
| 9U | 11 mm smooth | 11 mm smooth | R | Lysed | 5 days | Still resistant after 4 mo, bacteriophage in urine |
| 17U | 28 and 33 mm, green | 13 mm, colorless | R | Lysed | 7 days | Gradually in 2 mo, bacteriophage disappeared |
| 17U† | 13 mm velvety green | 5 mm colorless | R | Not lysed | 3 days | Gradually, bacteriophage disappeared |
| 24U | 45 mm, transparent | 1 mm, suicide | R | Lysed | Within 10 days | Gradually in 1 mo, no longer suicide |
| 36U | 14 mm, round | 19 mm, irregular | R | Lysed | 5 days | Patient died |
| 67U | 9 mm, irregular | 11 mm, round | R | Lysed | 56 hours | Sterile 8 weeks later |
| 74U | 13 and 21 mm, round | Suicide | * | * | 6 days | In 7 days, no bacteriophage in urine |
| 74U† | 13 mm, round | 39 mm, very irregular | Lysed | Lysed | 4 days | Sterile on eighth day |
| D | 55 mm, irregular | 2 mm suicide | * | * | By 11th day | Still suicide 31 days later |

* Could not be tested adequately due to spontaneous lysis of broth cultures

† Second treatment after reversion

maximum up to eight hours, in eighteen hours no difference from the controls could be detected. Patient 9U was treated twice without effect on the number of organisms or on the patient, from this experience the conclusion seems warranted that it is useless to administer a bacteriophage which cannot show some degree of permanent lysis in vitro.

The most frequent change in growth characteristics was the production of smaller colonies, sometimes even suicide cultures. With *B. pyocyaneus*, pigment production was lost, and the spreading tendency, transparency and the production of luster areas were lost, so that the culture gave a compact, regular, opaque colony. In two cases, the change revealed itself as a greater growth tendency with a larger colony usually spreading from one point to form an irregular shape.

Because the cultural characteristics remained the same and because the organism in a few instances was seen to revert to its original nature, these changes are considered to be true modifications and not a substitution of one infecting organism by another

In conclusion, it can be stated that during the treatment of patients with urinary infections by a bacteriophage built up on the causative organism, either the urine is sterilized or the organism is modified, at least in its susceptibility to that bacteriophage and usually, more profoundly, in its growth characteristics

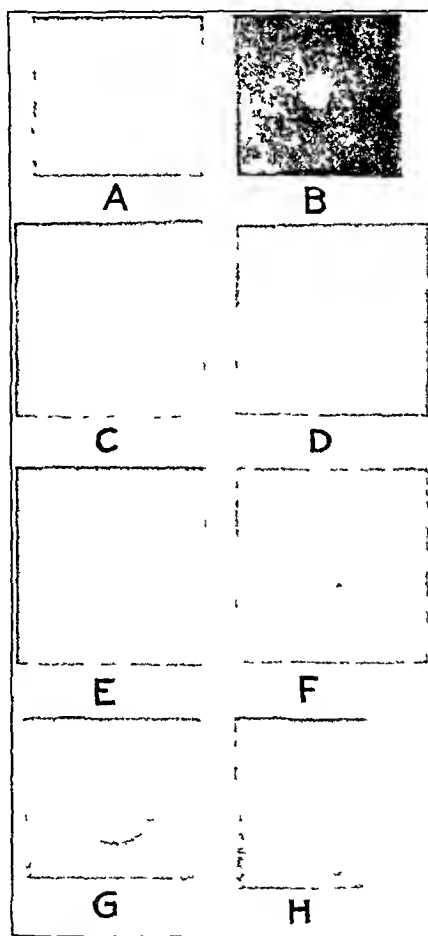


Fig 2—Growth modification in cultures following treatment *A* and *B* (case 24U) indicate growths before and after treatment The small colony is a typical "suicide" culture in broth *C* (case 17U) shows the original culture, large colony, green pigment, no bacteriophage in urine, *D*, the culture after treatment, small colony, no pigment, more opaque growth, resistant, bacteriophage in urine, *E*, the culture two months later showing partial reversion, colony larger, yellowish pigment, no bacteriophage in urine, *F*, the culture after second treatment, small colony, no pigment, resistant, bacteriophage in urine, *G* and *H* (case 36U), before and after treatment, note the greater growth activity following treatment This culture is now resistant and the bacteriophage is present in patient's urine in maximum strength

From these observations it is clear that the chief problem in the use of the bacteriophage in urinary infections is that of the ready adaptability of the organisms usually found in these cases so that they become resistant to the bacteriophage administered. The hope in this connection is the fact that resistance is individual—a resistance to only that one bacteriophage strain—and that the modified organism can be as readily lysed by a rich source of bacteriophage, sewage filtrate, as if it had not been in contact with a bacteriophage.

The prospect therefore, appears hopeful, but to combat the natural difficulty certain precautions seem essential. The bacteriophage used should not allow the early development of secondary cultures. It should be prepared and administered promptly, at frequent intervals and in adequate quantities locally so as to lyse the main bulk of organisms quickly thus preventing the modification which results in resistance. Cultures should be watched and if necessary re lysed by sewage filtrate and the second bacteriophage should be administered.

CONGENITAL MALFORMATIONS OF THE GALLBLADDER

REPORT OF THREE CASES OBSERVED BY CHOLECYSTOGRAPHY

SAMUEL LEVINE, M D

BROOKLYN

Any method of precision used in the diagnosis of disease has possibilities far surpassing its immediate application. The physician, however, is chiefly concerned with its immediate value to his patient. While this attitude is entirely commendable, the fact that a positive diagnostic method may become an instrument of investigation in the hands of the clinician should nevertheless be recognized. The application of radiology to the stomach has modified the conception of the anatomy of this organ. Radiology has added to the knowledge of gastric physiology, and has enabled physicians to observe the reactions of the stomach to drugs.¹ The clinician has thus been enabled to add considerably to the knowledge of the anatomy and physiology of the stomach and of the modifications of it caused by drugs. Radiology has, therefore, increased his usefulness to medicine and rendered him less dependent on the anatomist and on the experimenter with laboratory animals.

When cholecystography was introduced in medicine² the attention of physicians was directed almost entirely to its clinical value. So valuable a method however was predestined to wider usefulness. A method giving accurate information about the size, shape and position of the gallbladder and about its power of concentration and ability to empty its contents obviously will give valuable knowledge concerning its anatomy and physiology and concerning its response to drugs. Indeed, the question whether the gallbladder is a passive organ or whether it empties its contents by the contraction of its walls has already been solved by this method. Whitaker³ by experiments on animals and Levine⁴ by observations on man demonstrated contractions of the gallbladder by means of cholecystography. Clinicians should therefore be mindful of the opportunities for investigation inherent in positive diagnostic methods.

1 Assmann. *Klin. Röntgendiagnostik d. Inneren Erkrankungen*, ed. 3. Leipzig: F. C. W. Vogel, 1924. p. 400.

2 Graham, E. H. and Cole, W. H. Roentgenologic Examination of Gallbladder. New Method Utilizing Intravenous Injection of Tetratromphenolphthalein. *J. A. M. A.* 82: 613 (Feb. 23) 1924.

3 Whitaker, L. R. *Am. J. Physiol.* 78: 411, 1926. Diagnosis of Gallbladder Disease. *J. A. M. A.* 88: 1791 (June 4) 1927.

4 Levine, S. Contractions of Gallbladder Seen in Man, *Arch. Int. Med.* 40: 420 (Oct.) 1927.

Congenital anomalies of the gallbladder are frequent in animals, particularly in sheep, cattle and cats. They are said to be rare in man (Konjetzny⁵). Huber⁶ reported a case of congenital absence of the gallbladder "with preternatural enlargement of the hepatic duct." Double gallbladders were described by Sherren,⁷ Braun⁸ and Nichols.⁹ Diverticula of the gallbladder were reported by Courvoisier,¹⁰ by Staub¹¹ and by Sebening and Schondube.¹² In the case of the last named authors, the diverticulum was large enough to interfere with the emptying of the stomach. Of the twenty-eight cases mentioned by Courvoisier, eighteen patients had gallstones. A traction diverticulum was present only once. Hour-glass gallbladders were reported by Courvoisier, Hartmann,¹³ Malcolm,¹⁴ Morton¹⁵ and Torda.¹⁶ Malformations of the extrahepatic ducts are rather more frequent (Courvoisier,¹⁰ Konjetzny,⁵ Buzik,¹⁷ Meyenburg,¹⁸ Bohm,¹⁹ Budde,²⁰ Dreesman²¹). It is probable that cholecystography will add an interesting chapter to the study of anomalies of the gallbladder. With the exception of the case of Nichols,⁹ anomalies thus far reported have been observed only when the abdomen has been opened by either the surgeon or the pathologist. By means of cholecystography, however, physicians are able to study this condition in the living, ambulant patient, in whom this observation may be made accidentally. It is significant that in a rather small private practice, this method revealed three interesting anomalous gallbladders within a few months.

REPORT OF CASES

CASE 1—*Hour-glass gallbladder*

Mrs. S. S., aged 23, married eleven months, had never been pregnant. The history of menstruation was normal. Six months previous to her present

- 5 Konjetzny. *Ergebnisse allg. Pathol. u. path. Anat.* **14**: 712, 1910.
- 6 Huber. *Philosophic Transactions*, (abridged), London, 1744-1749, p. 649.
- 7 Sherren. *Ann. Surg.* **54**: 204, 1911.
- 8 Braun. *Zentralbl. f. Chir.* **53**: 1055, 1926.
- 9 Nichols. *Radiology* **6**: 255, 1926.
- 10 Courvoisier. *Casuistisch-statistische Beiträge zur Pathologie und Chirurgie des Gallenwege*, Leipzig, F. C. W. Vogel, 1890, p. 12.
- 11 Staub. *Cor.-Bl. f. Schweiz. Aerzte* **26**: 15, 1896.
- 12 Sebening and Schondube. *Arch. f. klin. Chir.* **137**: 308, 1925.
- 13 Hartmann. *Bull. Soc. anat. de Paris* **66**: 480, 1891.
- 14 Malcolm. *Proc. Roy. Soc. Med., Surgical Section*, part 3 **1**: 93, 1907-1908.
- 15 Morton. *Brit. M. J.* **2**: 1697, 1908.
- 16 Torda. *Arch. f. klin. Chir.* **100**: 1188, 1913.
- 17 Buzik. *Arch. f. Verdauungskr.* **22**: 370, 1916.
- 18 Meyenburg. *Virchows Arch. f. path. Anat.* **221**: 352, 1916.
- 19 Bohm. *Ztschr. f. ang. Anat.* **1**: 105, 1913-1914.
- 20 Budde. *Deutsche Ztschr. f. Chir.* **185**: 339, 1925, *München med. Wchnschr.* **72**: 848, 1925.
- 21 Dreesman. *Deutsche Ztschr. f. Chir.* **92**: 401, 1908.

illness she was in an automobile accident in which she sustained minor injuries to the right shoulder and right arm. The right ear drum was perforated during this accident. The patient came to my office on May 3, 1927, with the following history. The tonsils had been removed seven years before. One week after tonsillectomy, she had had an attack of acute abdominal pain which had been diagnosed as acute appendicitis. Operation had not been performed. Four weeks ago she had had diffuse abdominal pain which settled in the lower right quadrant of the abdomen. The pain still persisted in a milder form. It was cramplike in character and was not relieved by food. Occasional heartburn,

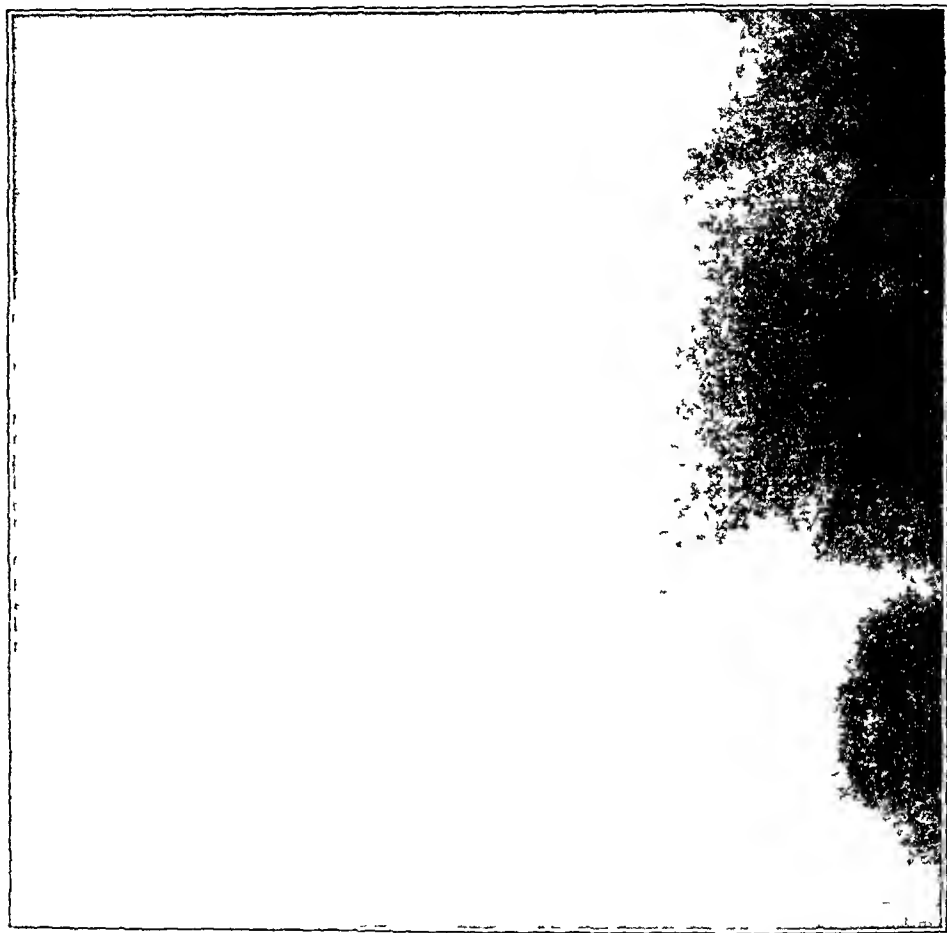


Fig 1 (case 1)—Cholecystogram of hour-glass gallbladder

independent of meals, was not relieved by food but was relieved by sodium bicarbonate. The patient belched considerably. Occasional pressure was present in the epigastrium. She did not vomit during or between attacks of pain. The bowels moved once in from one to two days without the aid of a cathartic.

The results of a physical examination were negative, with the exception of the observation of tenderness in the lower right quadrant of the abdomen. The blood count and blood chemistry did not reveal anything abnormal. The icteric index was 9.5 (normal from 4 to 6). One hour after an Ewald test meal the hydrochloric acid was 11, and the total acidity was 30. The urine and stool were normal. The blood Wassermann reaction was negative. Proctoscopic examination showed a normal rectum and sigmoid. The fluoroscopic

and roentgenographic examinations of the gastro-intestinal tract did not reveal any abnormalities, with the exception of constant tenderness in the lower right quadrant of the abdomen. The appendix was not visualized.

Fourteen hours after administration of the dye (tetraiodophenolphthalein sodium) by mouth, roentgenograms showed the gallbladder distinctly. At the junction of its middle and lower thirds, a circular constriction divided it into a wider upper and a narrower lower portion (fig 1). Ten minutes after

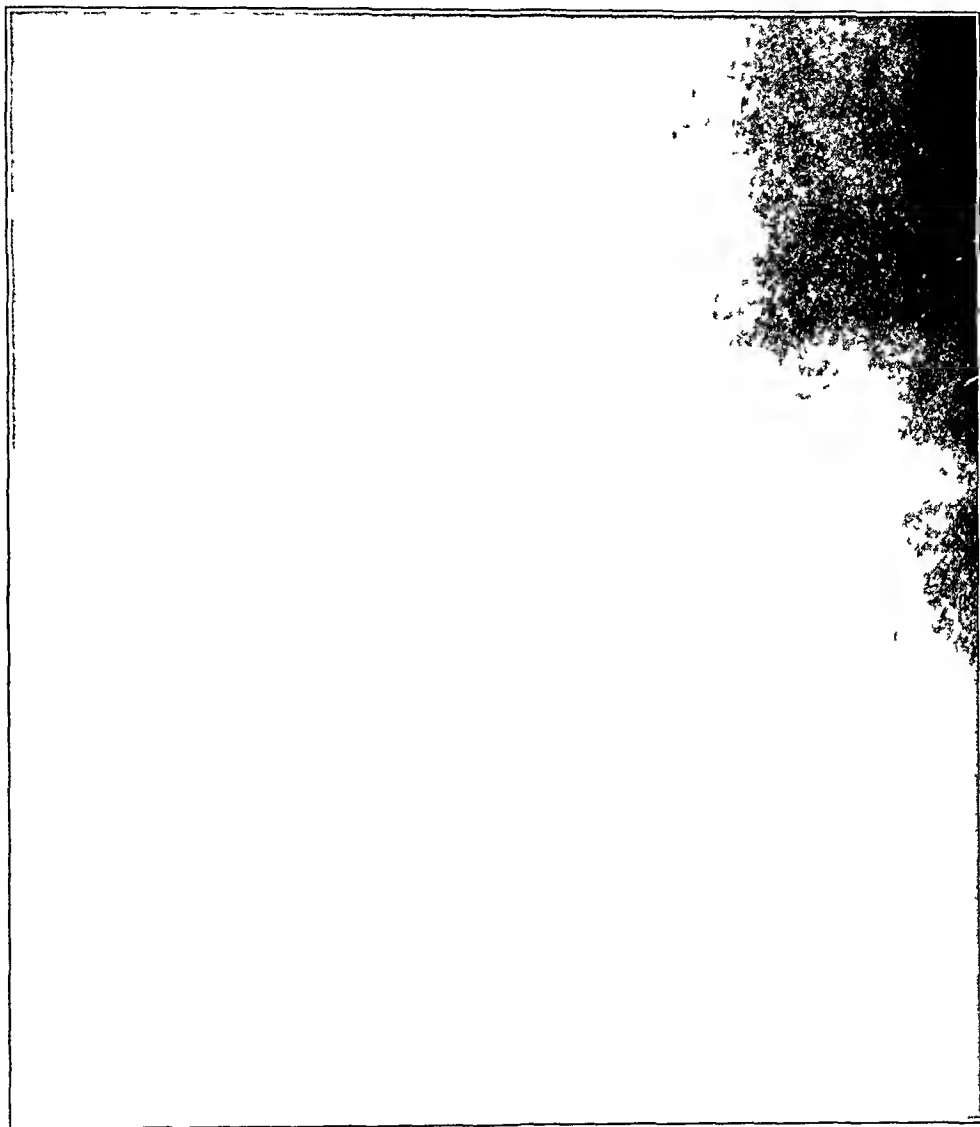


Fig 2 (case 1) —Hour-glass gallbladder about half its former size ten minutes after the ingestion of a fat meal. Proportionately, the lower cavity is diminished in size, even more than the upper.

the ingestion of a fat meal, the gallbladder was about half its former size (fig 2). Proportionately, the lower cavity had diminished in size even more than the upper. Two and a half hours after the administration of the dye, only a small speck of it was seen in the gallbladder (fig 3).

Morton's¹⁵ case did not show any evidence of cholecystitis, although stones were present in both the upper and the lower cavities, while in

Toida's¹⁶ case there was extensive inflammation of the lower portion of the gallbladder, but stones were not found. Both considered their cases as congenital in origin. Malcolm¹⁴ and Hartmann¹³ explained the hour-glass shape of the gallbladders in their cases by cicatricial con-

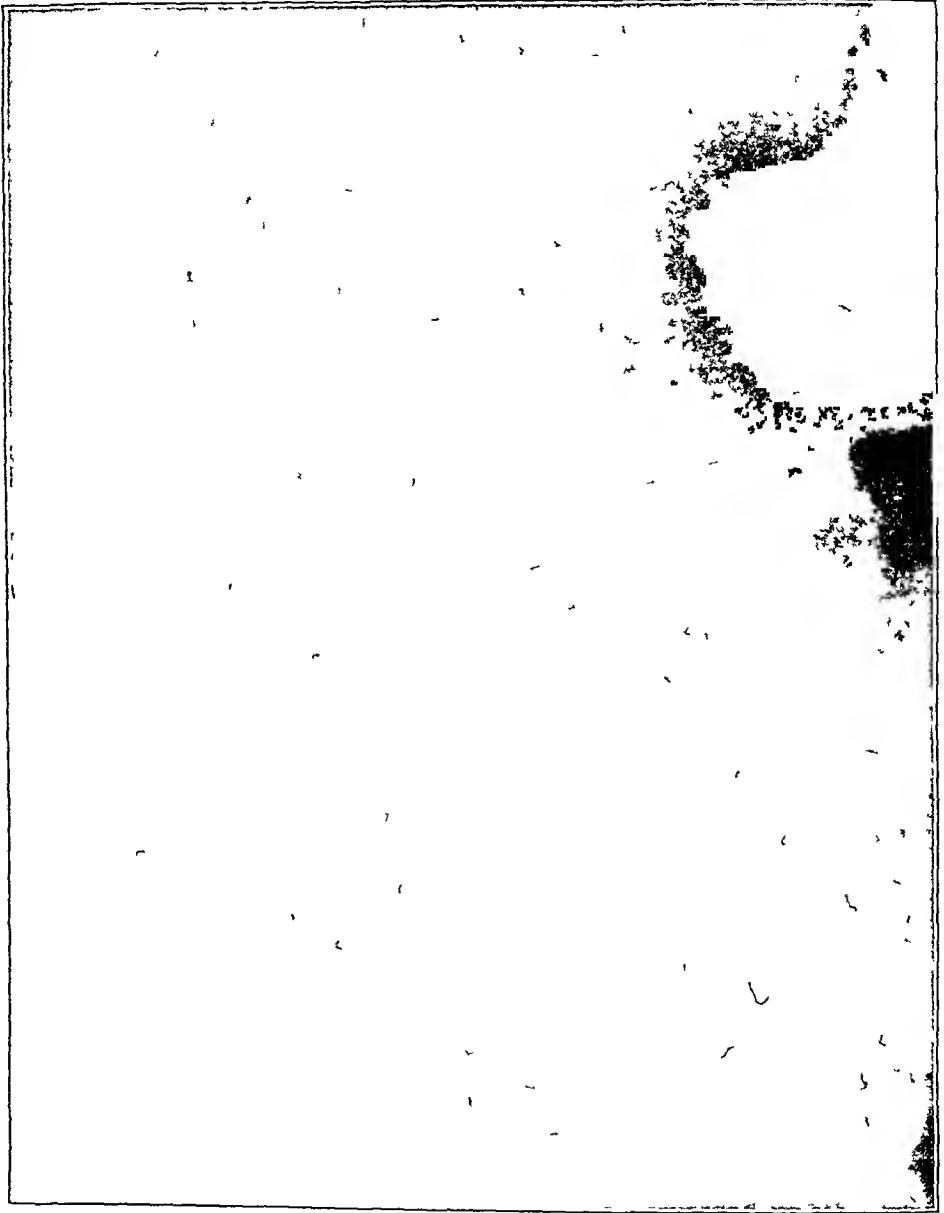


Fig. 3 (case 1) —Two and a half hours after the ingestion of a fat meal, only a small speck of dye is seen in the gallbladder

traction secondary to inflammation. In all of the fifteen cases compiled by Courvoisier,¹⁰ examination revealed either stones or definite traces of their presence at some former time.

In the case here reported, the origin of the condition is not entirely clear. The right-sided abdominal pain, pressure in the epigastrium,

belching and hypochlorhydria together with the high icteric index (9.5), favor the diagnosis of cholecystitis while the fact that the gallbladder concentrated and emptied in a normal manner speaks against this assumption. On the other hand the presence of cholecystitis does not rule out the congenital nature of its anomalous form. Inflammation and stone formation may develop as a result of the abnormal shape of the gallbladder which interferes with its emptying. In this case, however we were confronted by the fact that the gallbladder concentrated and emptied normally. Spasm can be ruled out, since the musculature of the gallbladder was arranged irregularly and a circular layer was not present (Aschoff and Bacmeister,²² Stohr-Mollendorf,²³ Lutkens²⁴). Whether there was any relation between the patient's recent accident and the hour-glass shape of the gallbladder is entirely problematic. Whatever pathologic conditions may be superimposed the congenital origin of this hour-glass gallbladder is plausible.

CASE 2—Gallbladder resembling a "Phrygian cap"

Mrs. F. L. aged 26, married for a period of three and a half years, had never been pregnant. Menstruation began at the age of 12 and occurred every twenty-eight days lasting three days. Three years previous to her present illness she stopped menstruating for six months since then menstruation had been normal. During the last two years she had suffered from weakness, excessive perspiration, palpitation and diarrhea (from four to five movements a day). Six months ago she experienced severe pain at the right costo-vertebral angle accompanied by dysuria and vomiting. Eleven weeks ago, and again seven weeks ago she was suddenly seized with cramps in the right lower quadrant of the abdomen. She did not vomit, but diarrhea persisted during these attacks.

The pulse rate was 120. The blood pressure was 98 systolic and 38 diastolic. The temperature was 99.4 F. There was marked tremor. A large goiter and exophthalmos were also present. Gräfe's sign was positive. Thrill was felt, and bruit was heard over the thyroid. Kyphosis of the thoracic spine was evident. A systolic murmur was heard over the precordium, and was transmitted to the vessels of the neck. Tenderness was marked over the upper left dorsal region and over the lower part of the precordium. The right lower quadrant of the abdomen was tender and rigid. Dermographia was marked. A tender mass was felt in the right vaginal fornix.

The basal metabolism was $+43$. Specimens of urine showed a trace of albumin and a few red and white blood cells. The blood count and blood chemistry did not reveal any abnormalities. The blood Wassermann reaction was negative. Fluoroscopic and roentgenographic examination of the gastrointestinal tract showed that the stomach was extended down one and a half

22 Aschoff and Bacmeister. Die Cholelithiasis, Jena, Gustav Fischer, 1909, p. 11.

23 Stohr-Mollendorf. Lehrbuch der Histologie, ed. 20, Jena, Gustav Fischer, 1924, p. 315.

24 Lutkens. Aufbau und Funktion der extrahepatischen Gallenwege, Leipzig, F. C. W. Vogel, 1926, p. 77.

handbreadths below the crest of the ilium, the incisura angularis was two fingerbreadths below. Tenderness was present to the right of the umbilicus. After four hours, the stomach was empty, and after twenty-four hours, the entire gastro-intestinal tract was empty, but the appendix was filled. It was irregular in outline and beaded.



Fig. 4 (case 2)—Cholecystogram of gallbladder resembling a "Phrygian cap." Note the notch between the body and the ampulla.

Fourteen hours after the administration of the dye (tetraiodophenolphthalein sodium) by mouth roentgenograms showed the gallbladder clearly (fig. 4). Its lower pole was bent upward and toward the spine. Two hours after the ingestion of a fat meal, the gallbladder was empty.

In 1916, Bartel²⁵ described three anomalous gallbladders observed at autopsy. In each case the lower pole was bent upward in such a way as to suggest a "Phrygian cap." One was that of a girl, aged 15, with diabetes mellitus, the second, that of a woman, aged 30, with syphilis of the liver and of the aorta, and the third that of a woman, aged 41, with tuberculosis of the lungs and peritoneum. All three had cholesterol stones in the gallbladder. Two years later,²⁶ this author reported forty more autopsies in which the same or similar anomalies in the shape of the gallbladder were observed. Six of his forty-three patients had pure cholesterol stones and one had an inflammatory stone. From a study of the clinical histories and pathologic observations in these cases, he came to the conclusion that such a gallbladder is a sign of constitutional inferiority. It is often associated with lymphatism, status thymico-lymphaticus, hernia, genital hypoplasia and a narrow aorta, and it predisposes to tuberculosis, syphilis, cystic ovaries and adenomatous goiter.

The gallbladder of the patient in the case under consideration seems to answer to Bartel's description, although his articles do not contain any photographs. It is significant that this patient was never pregnant, although she had been married for three and a half years, that three years before she stopped menstruating for six months, and that she was suffering with hyperthyroidism. In 1913, Chvostek²⁷ emphasized the fact that the constitution of the patient plays a great rôle in the development of this disease.

CASE 3—*Rudimentary gallbladder*

A. L., a man, aged 22, a clerk, single, during the last ten months had had burning pain in the epigastrium which was relieved for one hour by food. The patient did not have cramps. On physical examination, the pulse rate was 96, the blood pressure was 128 systolic and 80 diastolic. A soft systolic murmur was heard over the base of the heart. Abdominal tenderness was not present. Both inguinal rings were large. The urine, stool and Ewald test meal were normal. The blood count was normal, except for an increase in the lymphocytes (46 per cent). The icteric index was 82. The blood Wassermann reaction was negative. Fluoroscopic and roentgenographic examination of the gastro-intestinal tract revealed a moderately ptosed stomach. The appendix remained filled forty-eight hours after a barium meal. At that time the rest of the large intestine was empty.

Twelve hours after the administration of the dye (tetraiodophenolphthalein sodium) by mouth, roentgenograms showed the gallbladder distinctly. It was about one-third the normal size and conical, and its fundus tapered to a point (fig. 5). Two hours after the ingestion of a fat meal, it was still about one-half full (fig. 6).

Endocrinologic and neurologic examinations (by Dr. William Leavitt) showed the following. The patient's height was 73.3 inches, the weight was

25 Bartel. Frankfurt Ztschr. f. Path. **1-2** 206, 1916.

26 Bartel. Wien klin. Wchnschr. **31** 605, 1918.

27 Chvostek. Ztschr. f. ang. Anat. **1** 27, 1913.

165 pounds (178 Kg) The circumference of the head, which was large and brachycephalic, was 22 inches The cephalic index was $87 +$ His bones were long, and he was long-waisted The skin was fair and fine There was moderate growth of hair over the upper part of the chest, anteriorly and posteriorly The pubic hair was of the male type of distribution The face

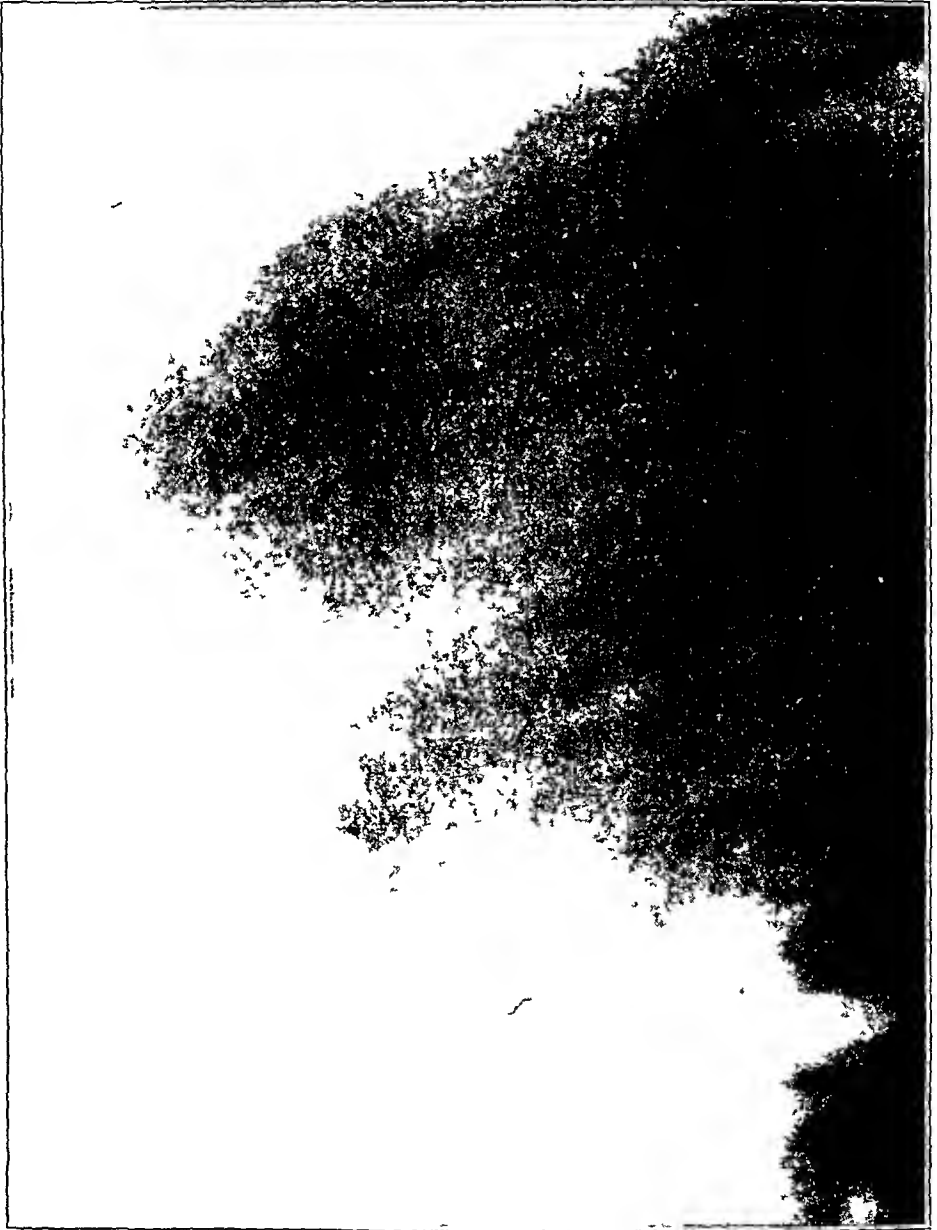


Fig 5 (case 3) —Cholecystogram of rudimentary gallbladder, conical in shape, with fundus tapering to a point

was long, the nose was sharp, prominent and thin The eyeballs were deeply set The palate was high and arched and the teeth were regularly set The neck was long, thin and strong, but not massive He had cyanosis of the hands and feet, but they were warm and moist The lower part of the abdomen was prominent, suggesting visceroptosis The genital organs were normal

The results of the neurologic examination were negative. The patient was shy, and had a hesitant personality. He was of normal intelligence but lacked aggressiveness. He was passive and docile, and found it difficult to make advances. It is significant that he had a lymphocyte count of 46 per cent. The impression was that the abnormal development was of the "thymic type."

Rudimentary gallbladders about the size of a goose quill are described by Cursham,²⁸ Wilks²⁹ and Roth³⁰. These extreme cases,



Fig 6 (case 3)—Two hours after the ingestion of a fat meal, the gallbladder is about one-half full.

however, are usually accompanied by obliteration of the bile ducts with subsequent development of jaundice and biliary cirrhosis, terminating in death in early infancy. The case under consideration answers fairly

28 Cursham. *London Med Gaz* **26**² 388, 1840.

29 Wilks. *Tr Path Soc London* **13** 119, 1862.

30 Roth. *Virchows Arch f path Anat* **43** 296, 1868.

well to what Berg ³¹ calls 'the gallbladder of rudimentary morphology'. In this condition the gallbladder is less differentiated from the cystic duct more mobile, and its emptying power is impaired. Therefore a disturbance is produced in the pressure regulation of the entire hepatic system, which may lead to deranged hepatic function. In this case the small size of the gallbladder its conical shape, impaired power of concentration and delayed emptying time are the anatomic and physiologic evidences of abnormal structure and function. The high icteric index (82) suggests disturbed hepatic function. The age of the patient and the history of the case do not warrant the assumption that these deviations from the normal are due to pathologic changes in the gallbladder. On the contrary his entire make-up, as evidenced by his somatic and mental characteristics, strongly suggests the presence of developmental disturbances which are also the probable causes of this abnormal gallbladder.

EMBRYOLOGY OF THE GALLBLADDER

Felix ³² and Hammar ³³ thought that the liver and its ducts develop simultaneously from the protrusion at the ventral portion of the foregut, that the cranial portion of this protrusion forms the liver and its caudal portion, the ducts. This has been definitely disproved by Ludwig, ³⁴ according to him only the liver is formed by the protrusion. However, as it moves away from the foregut it remains united to it by a strand which undergoes canalization and forms the primitive common bile duct. This is still lined with liver cells which subsequently become the glands of the ducts. The primitive gallbladder is formed by a depression in this duct, the permanent gallbladder arises by the formation of a bud in this depression. The cells in this bud proliferate and give rise to a number of cavities each separated from its neighbors by septums. Eventually they fuse and form one cavity. The primary gallbladder becomes the cystic duct. The permanent gallbladder is not lined by liver cells and therefore does not contain glands (Aschoff and Bacmeister ³⁵). When the cavities fail to fuse properly various congenital anomalies may arise.

SUMMARY

1. Methods of precision used in the diagnosis of disease may become useful instruments of investigation in the hands of the clinician. This is illustrated by the contributions of roentgenology to the knowledge of

31 Berg Arch f klin Chir 126 327 1923

32 Felix Arch f Anat u Physiol 1892 p 281

33 Hammar Arch f Anat u Physiol 1893 p 123

34 Ludwig Anat Hefte First Part 56 513, 1918-1919

35 Aschoff and Bacmeister Die Cholelithiasis, Jena, Gustav Fischer, 1909, p 17

the anatomy and physiology of the stomach and its response to drugs. It is further illustrated by the valuable information gained in the physiology of the gallbladder since the introduction of cholecystography in clinical medicine.

2 Three anomalous gallbladders, most likely of congenital origin, are described. In the course of routine examinations, these were detected by means of cholecystography. The three types are:

(a) Hour-glass gallbladder. This case is most likely of congenital origin.

(b) Gallbladder resembling a "Phrygian cap." This is associated with hyperthyroidism, menstrual irregularity and sterility. It is therefore considered part of a general constitutional disturbance.

(c) Rudimentary gallbladder. This answers the description of Beig's "gallbladder of rudimentary morphology." The patient also conforms to that variety of abnormal development known as the "thymic type."

ELECTIVE LOCALIZATION OF STREPTOCOCCI ISOLATED FROM CASES OF PEPTIC ULCER *

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As yet there is no universal agreement concerning the pathogenesis of the peptic ulcer which occurs spontaneously in man. Voluminous articles have been devoted to the effort to establish some causative factors, but the various theories and experimental reports have generally led rather to divergence than to convergence of ideas as to the particular etiologic agent.

It is true that ulcerations in the gastric and duodenal mucosa have been produced in various ways, but these experimental methods are usually so foreign to what could actually occur clinically that they can have little practical bearing on the etiology of the ulcer in man.

REVIEW OF THE LITERATURE

Ulcers of the stomach have been produced experimentally by interfering with nerve supply,¹ by section of the spinal cord² and by section or stimulation of the vagus or the sympathetic nerves. Durante³ and Vedova⁴ by such methods produced fairly well formed ulcers in a considerable number of experiments. Similarly, lesions have been produced by injuring the mucosa mechanically, by excising pieces, by the use of sutures,⁵ by the application of the actual cautery or silver nitrate and nitric acid,⁶ by injecting into or beneath the mucosa such substances as

* From the Division of Experimental Bacteriology, The Mayo Foundation

1 Stahnke, Ernst. Experimentelle Untersuchungen zur Frage der neurogenen Entstehung des Ulcus ventriculi zugleich ein Beitrag zur pathologischen Physiologie der Mageninnervation, *Arch f klin Chir* **132** 1, 1924

2 Kawamura, K. Ueber die experimentelle Erzeugung von Magengeschwüren durch Nervenlasionen, *Deutsche Ztschr f Chir* **109** 540, 1911

3 Durante, Luigi. The Trophic Element in Origin of Gastric Ulcer, *Surg Gynec Obst* **12** 399, 1916

4 Vedova, R. D. Ricerche sperimentali sulla patogenesi dell' 'ulcera gastrica, *Policlinico* **6** 1153, 1899-1900

5 Katzenstein, M. Beitrag zur Entstehung des Magengeschwurs, *Arch f klin Chir* **101** 1, 1913

6 Quincke, H., and Daetwyler. Untersuchungen über Magengeschwüre, *Cor-Bl f schweiz Aerzte* **5** 101, 1875

foreign protein in sensitized animals,⁷ gastrotoxic serum,⁸ silver nitrate⁹ and alcohol,¹⁰ by the injection of lead chromate¹¹ and fat¹² to produce embolic lesions, by intravenous injection of poisons such as pilocarpine, phenol, chloroform, bile salts,¹³ B-tetra-hydronophthylamine,¹⁴ epinephrine,¹⁵ diphtheria toxin¹⁶ and filtrates of various bacteria and by extirpation of the suprarenal and thyroid glands¹⁷. Some have maintained that ulcers may be due to a disproportion between the gastric pepsin and the antipepsin of the blood serum¹⁸. Mann and Williamson¹⁹ produced single subacute and chronic ulcers in the jejunum of dogs in a high percentage of cases when anastomosis of the jejunum to the stomach was performed and when the duodenum with its alkaline content was drained into the terminal ileum. Ulcerations have been produced in many sites in the stomach by

7 Ivy, A. C., and Shapiro, P. F. Experimental Production of Gastric Ulcer by Local Allergy, Preliminary Report, *J. A. M. A.* **85** 1131 (Oct. 10) 1925

8 Bolton, Charles. Experimental Production of Gastric Ulceration by Injection of Gastrotoxin, *Lancet* **1** 1330, 1908

9 Friedman, J. C., and Hamburger, W. W. Experimental Chronic Gastric Ulcer, *J. A. M. A.* **63** 380 (Aug. 1) 1914

10 Licini, Cesare. Ueber experimentelle Erzeugung von Magengeschwüren, *Beitr. z. klin. Chir.* **79** 462, 1912

11 Cohnheim, J. F. Lectures on General Pathology, London, New Sydenham Society **3** 879, 1890

12 Schridde. Experimentell erzeugte Magengeschwüre bei Merschweinchen (Diskussion), *Verhandl. d. deutsch. path. Gesellsch.* **11** 234, 1907

13 Sellards, A. W. Ulceration of the Stomach and Necrosis of Salivary Glands Resulting from Experimental Injection of Bile Salts, *Arch. Int. Med.* **4** 502 (Nov.) 1909. Smith, G. M. An Experimental Study of the Relation of Bile to Ulceration of the Mucous Membrane of the Stomach, *J. M. Research* **30** 147, 1914

14 Elliott, T. R. The Experimental Formation of Acute Gastric Ulcers, *Quart. J. Med.* **7** 119, 1914

15 Friedman, G. A. The Influence of Removal of Adrenals and One Sided Thyroidectomy upon the Gastric and Duodenal Mucosa, the Experimental Production of Lesions, Erosions, and Acute Ulcer, *J. M. Research* **32** 287, 1915. Probable Endocrine Origin of Peptic Ulcer, *New York M. J.* **107** 1205, 1918

16 Rosenau, M. J., and Anderson, J. F. A Stomach Lesion in Guinea Pigs Caused by Diphtheria Toxin and Its Bearing upon Experimental Gastric Ulcer, *J. Infect. Dis.* **4** 1, 1907

17 Carlson, A. J., and Jacobson, Clara. Further Studies on the Nature of Parathyroid Tetany, *Am. J. Physiol.* **28** 133, 1911. Mann, F. C. A Study of the Gastric Ulcers Following Removal of the Adrenals, *J. Exper. Med.* **23** 203, 1916. Also see footnote 15

18 Einstein, Otto. Ueber die verdauungshemmende Wirkung von Antipepsin des Blutserums bei Magengesunden und Magengeschwurskranken, *Med. Klin.* **20** 1578, 1924. Leiblein, Viktor. Ueber den Antipepsingehalt des Blutes in Fällen von *ulcus ventriculi*, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **25** 391, 1912

19 Mann, F. C., and Williamson, C. S. The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77** 409, 1923

roentgen rays ²⁰ In 1853 Virchow ²¹ initiated the idea, which has been accepted by many, that spasms or portal stasis might give rise to hemorrhagic infarction and subsequent ulceration Various functional disturbances of the stomach, such as hypotonia and hypertonia, have supposedly produced lessened resistance by interfering with the nerve or blood supply, and thus have led to the formation of ulcer by subsequent digestion ²² Hamburger ²³ stated that abrasions resulting from traumatization by food or from emboli or bacteria produce acute ulceration which in the presence of hypersecretion and hyperacidity from some underlying cause, such as vagotonia or reflex pylorospasm, may produce chronic ulcers Morris ²⁴ stated that the ulcer probably starts with a proliferating endarteritis due to some toxic excretion and suggests *Bacillus coli* as the possible toxic agent Wilkie, ²⁵ from postmortem study, concludes that toxic absorption from the appendix or colon could produce an irritable condition of the autonomic nervous system with tendency to ulcer formation The relation of infection to the formation of ulcer has been demonstrated by many clinical and experimental investigations It has infrequently been noticed that ulcers of the stomach occur during severe and fatal infections, particularly those of streptococcic origin Intravenous injection of pus by Leber ²⁶ and Cohn ²⁷ and of streptococci and staphylococci by Letulle ²⁸ produced similar lesions as did also the pneumococci injected by Bézancón and Giffon ²⁹ Boettcher ³⁰ in 1874 demonstrated bacteria in the edges and floor of ulcers, and Dudgeon and

20 Wolfer, J A Chronic Experimental Ulcer of the Stomach, Its Clinical Significance, *J A M A* **87** 725 (Sept 4) 1926

21 Virchow, Rudolph Historisches Kritisches und Positives zur Lehr der Unterleibs Affektionen, *Arch f path Anat u Physiol* **5** 281, 1853

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28 Letulle, M Origine infectieuse de certains ulcères simples de l'estomac ou du duodenum, *Bull et mem Soc med d hôp de Paris* **5** 360, 1888

29 Bézancón, F, and Giffon, V Ulcerations gastriques au cours de la septicémie pneumococcique chez le cobaye, *Bull et mem Soc anat de Paris* **1** 409, 1899

30 Boettcher, H Zur Genese des perforirenden Magengeschwurs, *Dorpat med Ztschr* **5** 148, 1874

Sargent³¹ isolated a diplostreptococcus from the edges of ulcers and peritoneal exudate in four cases of ulcer after death from perforation. Steinharter³² reported his work on the production of gastric ulcers and duodenal hemorrhagic lesions by the injection of clumped colon bacilli. Türk³³ claimed to have found typical round ulcers of the stomach and duodenum in dogs after they had been fed colon bacilli for a long period. Hoffman³⁴ isolated an aerobic nonmotile bacillus from the tonsils and gastric contents in a few patients who had ulcers and claimed to have produced ulcers in animals with the organism and its filtrate.

Whether a focus of infection usually symptomless and apparently harmless in itself can under certain conditions act as a distributing center for micro-organisms which have acquired particular evasive and localizing power and produce in distant places acute sub-acute or chronic inflammatory lesions is an interesting as well as a much discussed problem. As long ago as 1801 Benjamin Rush³⁵ noted a relationship between infected teeth and systemic disease. However little attention was paid to it until Billings³⁶, Rosenow³⁷ and their co-workers made extensive clinical and experimental investigations of this question. Rosenow in 1913 reported experiments in which it was found that the intravenous injection of streptococci of proper grade of virulence may be followed by ulcer of the stomach and duodenum; this ulceration is due to localized infection and secondary digestion. On the basis of these experiments the theory that the usual form of gastroduodenal ulcer may be due to a localized infection by streptococci having elective affinity for the mucous membrane of the stomach and duodenum took definite form. In a series of subsequent studies much evidence

31 Dudgeon L. S. and Sargent P. W. The Erasmus Wilson Lectures on Peritonitis. A Bacteriological Study. *Lancet* 1:473 1905.

32 Steinharter E. C. A Preliminary Note on the Experimental Production of Gastric Ulcers by Intravenous Injection of Clumped Colon Bacilli. *Boston M. & S. J.* 169:81 1913.

33 Türk F. B. Further Observations on the Etiology and Pathology of Peptic Ulcer. *Brit. M. J.* 1:922 1907.

34 Hoffman Albert. Experimental Gastric and Duodenal Inflammation and Ulcer Produced with Specific Organism Fulfilling Koch's Postulates. *Am. J. M. Sc.* 170:212 1925.

35 Rush Benjamin quoted by Dacre W. W. Oral Sepsis in Its Relation to Systemic Disease. St. Louis C. V. Mosby Company 1918 p. 124.

36 Billings Frank. Chronic Infectious Endocarditis. *Arch. Int. Med.* 4:409 (Nov.) 1909.

37 Rosenow E. C. The Production of Ulcer of the Stomach by the Injection of Streptococci. *J. A. M. A.* 61:1947 (Nov. 29) 1913. The Causation of Gastric and Duodenal Ulcer by Streptococci. *J. Infect. Dis.* 19:333 1916. Specificity of Streptococcus of Gastroduodenal Ulcer and Certain Factors Determining Its Localization. *J. Infect. Dis.* 33:248 1923. Studies on Elective Localization. Focal Infection with Special Reference to Oral Sepsis. *J. Dent. Res.* 1:205 1919.

in support of this theory has been reported. In 1914, Rosenow and Sanford reported the observation of diplococci in the tissues in a series of chronic ulcers excised at operation. Rosenow, in 1915, reported the isolation of streptococci (from excised ulcers and from foci of infection in patients suffering from peptic ulcer) which had elective affinity for the stomach and duodenum when injected intravenously into animals and which produced hemorrhage and ulceration in a high percentage of these animals. He also showed that this did not occur with streptococci obtained from the metastatic lesions and from foci of infection in patients free from ulcer. In a further experimental study with streptococci from ulcer, reported in 1916, he showed that the ulcers produced by the injection of streptococci resembled the ulcers of man in situation, in gross and microscopic appearance and in their tendency to perforate and to persist along the lesser curvature, in the pylorus and in the first part of the duodenum. The streptococcus was frequently demonstrated microscopically in the hemorrhagic and ulcerated areas, not only in the lesions of the stomach and duodenum of animals injected intravenously with the ulcer-producing streptococcus but also in the chronic jejunal ulcers of dogs. Rosenow also isolated a similar streptococcus from spontaneous ulcers of the stomach of the dog, calf, cow, sheep and swine, which had elective affinity for the stomach of animals when injected intravenously. It is also of significance that in five of seven chronic jejunal ulcers in dogs produced by the duodenal drainage method of Mann and Williamson, he also was able to isolate a streptococcus with similar selective action.

In 1923, he again published further corroborative data showing that the ulcer-forming streptococcus produces a poison within itself and also a free poison in broth cultures which, when injected, injures selectively the gastric and duodenal mucosa and produces hemorrhage, leukocytic infiltration and ulceration. By immunizing one group of rabbits to ulcer strains and another group to encephalitis strains of streptococci, and then injecting all the rabbits with vulnerable doses of living ulcer-forming streptococci, he found that ulcers did not form in the animals immunized to the ulcer strains whereas they did appear in the control rabbits immunized to encephalitis strains. He also found that rabbits immunized to ulcer-producing streptococci obtained from the ulcers in dogs were immune to the ulcer-producing streptococci obtained from ulcers in man.

Meisser,³⁸ working with the streptococcus from oral foci of infection, was able to show that in animals injected intravenously with these organisms lesions usually developed which were similar to those of the patient,

38 Meisser, J. G. Further Studies on Elective Localization of Bacteria from Infected Teeth, *J. Am. Dent. Assn.* **12** 554, 1925.

while the injection of equally large doses of streptococci from the saliva or mucosa of the mouth in most instances failed to produce any specific lesions. He also produced chronic foci of infection in dogs by devitalizing and infecting their four cuspids with streptococci isolated from the infected teeth of patients suffering from ulcer of the stomach. In 65 per cent of these dogs hemorrhages or ulceration or both were produced. Section of some of these areas showed definite scarring and other evidences of chronicity. Of thirty-four dogs in which Rosenow and Meisser infected the teeth in exactly the same manner with strains of streptococci from nine patients suffering from nephrolithiasis, thirty developed lesions in the genito-urinary tract. In none were any gastroduodenal lesions produced.

Haden³⁹ reported a series of twelve cases of peptic ulcer in which he made a study of foci of infection in dental areas, and he obtained localization in the stomach and duodenum in 53 per cent of forty-five rabbits injected. For control, 535 rabbits were injected intravenously with cultures from dental foci of patients not known to be suffering from peptic ulcer, similar lesions were manifested in only 7 per cent of the rabbits given these injections.

Nakamura,⁴⁰ studying elective localization in cases of ulcer of the stomach in Rosenow's laboratory, found gross evidence of infection of the tonsils in nine selected cases of gastric or duodenal ulcer. In forty-six (70 per cent) of the rabbits injected with the strains isolated from the tonsils of the nine patients, hemorrhages or ulceration or both were found in the mucous membrane of the stomach or duodenum, in contrast to lesions of the joints in 30 per cent, of the muscles in 2 per cent, of the heart in 6 per cent and of the kidneys in 4.5 per cent.

Frick⁴¹ stated that according to his clinical experience there seems to be no doubt that Rosenow's theory of the elective affinity of a specific streptococcus, of a certain grade of virulence, for the gastric or duodenal mucosa is correct and that a specific streptococcus is the common cause of peptic ulcer.

In the wall of a duodenal ulcer which was the source of hemorrhage in an infant dying with melena neonatorum, Kennedy⁴² demonstrated gram-positive streptococci, morphologically like those found in ulcers in men.

39 Haden, R. L. The Elective Localization of Bacteria in Peptic Ulcer, *Arch Int Med* **35**:457 (April) 1925. Haden and Bohan, P. T. Focal Infection in Peptic Ulcer, *J A M A* **84**:409 (Feb 7) 1925.

40 Nakamura, T. A Study of Focal Infection and Elective Localization in Ulcer of the Stomach and in Arthritis, *Ann Surg* **79**:29, 1924.

41 Frick, Anders. Medical Treatment of Peptic Ulcer Without Alkali, *J A M A* **82**:595 (Feb 23) 1924.

42 Kennedy, R. L. J. Etiology and Healing Process of Duodenal Ulcer in Melena Neonatorum, *Am J Dis Child* **31**:631 (May) 1926.

Smithies ⁴³ stated that 33 per cent of his 522 proved cases of gastric ulcer were infectious in origin. White ⁴⁴ and Stewart ⁴⁵ stated that as a result of all evidence presented, they believed that infection and intoxication are the most important direct causes of acute ulcer. Eusterman ⁴⁶ summarized the clinical evidence for the infectious origin of peptic ulcer in the light of recent experimental work and expressed the opinion that in certain types of ulcer it is the only tenable theory at this stage of medical progress.

Certain recent observations of foreign investigators on the resected ulcer of man corroborate the work done in this country. Konjetzney ⁴⁷ found a high percentage of gastritis or duodenitis about these resected ulcers, and Kalima found evidence of gastritis in all resected specimens of ulcer. Puhl ⁴⁸ showed that all cases of peptic ulcer are accompanied by gastritis or duodenitis of more or less severity, most marked in the region of the pyloric glands. In his series of 140 resected gastric and duodenal ulcers, he found numerous small erosions even far distal to the chronic ulcer, superimposed on an inflammatory process. There were all gradations from the acute hemorrhagic erosion to the chronic ulceration. He was therefore inclined to believe that the same factors which initiated one initiated the other. He was able to demonstrate bacteria in the sections, chiefly gram-positive diplococci, but was unable to culture any of them, and therefore did not draw any definite conclusions concerning them.

In a recent paper, Moutier ⁴⁹ said that he had been able to demonstrate the diplostreptococcus deep in the inflammatory zone surrounding the ulcer. He said that since the organisms are most numerous adjacent to the muscularis, they cannot be the result of contamination, and that therefore certain peptic ulcers at least are infectious in origin.

The mass of accumulated data, both clinical and experimental, shows that the probable cause of ulcer is still a subject of much debate among clinicians. It is universally agreed that the fundamental change *per se* in the gastric or duodenal mucosa is impaired nutrition in a localized

43 Smithies, Frank. Significance of Etiologic Factors in the Treatment of Peptic Ulcer, *J A M A* **74** 1555 (June 5) 1920.

44 White, F W. The Etiology and Pathology of Perforating Gastric and Duodenal Ulcer, Boston *M & S J* **177** 555, 1917.

45 Stewart, M J. The Pathology of Gastric Ulcer, *Brit M J* **2** 955, 1923.

46 Eusterman, G B. Clinical Notes on Recurrent Ulcer of the Stomach and Duodenum, Incidence, Diagnosis and Etiology, *Minnesota Med* **6** 698, 1923.

47 Konjetzney, G E. Die chronische Gastritis des Ulcusmagens, *Zentralbl f Chir* **1** 1026, 1923.

48 Puhl, Hugo. Ueber die Bedeutung entzündlicher Prozesse für die Entstehung des Ulcus ventriculi et duodeni, *Arch f path Anat u Physiol* **260** 1, 1926.

49 Moutier, F. Étude anatomo pathologique. Les étapes infectieuses de l'ulcère, *Arch d mal de l'app digestif* **16** 18, 1926.

area with subsequent necrosis, sloughing and digestion in the injured area by the corrosive action of the acid gastric juice. The mechanical, corrosive, thrombotic, embolic and neurogenic factors are emphasized by the exponents of the different theories. The theory of infection, however, has gained more prominence in recent years chiefly as a result of the work of Rosenow and his co-workers, yet all gastro-enterologists do not grant that the chief cause of ulcer is a specific streptococcus, although the vast majority consider the focus of infection as at least partly responsible.

One of the best proofs of a causal relationship of bacteria to systemic disease is the reproduction of the patient's lesion in animals by the injection of the organisms isolated from the lesion or the septic foci of the patient. Ability to reproduce the lesions in this way not only clarifies the etiology, but demonstrates the specificity of certain organisms for a particular type of tissue which Rosenow has so aptly termed "elective localization."

EXPERIMENTAL INVESTIGATION

The present investigation was undertaken to prove or disprove certain impressions gained in a study of peptic ulcer which seemed to have an important bearing on the etiology of clinical peptic ulcer. As the work of Rosenow and of others who have followed his technic has shown conclusively that a specific streptococcus is harbored by the patient suffering from ulcer, and that when isolated and inoculated into animals this organism will produce lesions similar to those in man, and since in many cases of primary or recurring ulcer there is rather marked evidence of focal infection, two groups of cases of ulcer were studied. In one group, a series of consecutive cases extending over a period of six months was studied to determine whether streptococci were being harbored in every case, this was done so far as such investigation was permitted and desirable clinically. The next step was to determine whether acute and subacute lesions could be reproduced in animals by intravenous injection, and chronic lesions by inoculating the organisms into the devitalized teeth of dogs. In the second series of eleven cases of peptic ulcer resected at operation, the resected ulcers as well as the suspected foci were carefully investigated for ulcer-producing streptococci.

Technic—The method of obtaining the culture varied with the focus. If the focus was the tonsil, a culture was obtained by using a small laryngeal mirror with the mirror so bent as to be almost in a straight line with the handle. The tongue was depressed with an illuminated tongue depressor and the sterilized laryngeal mirror was then inserted between the tonsil and the anterior pillar, and pressure applied backward and mesially toward the base of the tonsil. This procedure caused necrotic and puslike material to ooze from the depths of the crypts, the material was then scooped up with the laryngeal mirror and transferred with

a sterile swab from the mirror to a tube containing 2 cc of gelatin-Locke solution, from which cultures were made in various mediums

If the focus was a tooth, the operative field was wiped off with sterile gauze, painted with 2 per cent iodine followed by alcohol, and then dried with sterile gauze. The tooth was then extracted with sterile forceps, and while still held in the forceps, its apical one-fourth was nipped off with sterile nippers into small tubes containing Locke's solution and white sand, according to Haden's method. This was shaken for ten or fifteen minutes and then inoculated into the various culture mediums.

If the focus was the prostate, the glans was washed with soap and water followed by a sterile solution of physiologic sodium chloride. Then the posterior and anterior urethra were copiously irrigated with a similar sterile solution. The prostate was then massaged and the expressed material caught directly in tubes containing gelatin-Locke solution for culture. If the cervix was the suspected focus, a sterile speculum was used, a sterile swab was used to wipe off the external part and to secure superficial micro-organisms, while a second one was inserted into the canal or any eroded places for a culture.

The surgically resected peptic ulcers were cultured immediately after being excised. A portion of the ulcer was thoroughly shaken in three changes of sterile solution of sodium chloride to remove as much superficial contamination as possible, then emulsified in a sterile manner in a mortar with white sand and 4 cc of sodium chloride solution, cultures were then made from this emulsion. All of the cultures were plated aerobically on blood-agar plates, and inoculated into glucose-brain agar and glucose-brain broth with and without a top layer of petrolatum (not liquid petrolatum) made according to Rosenow's method.

The blood-agar plate served as a control, especially in cultures from teeth, because the large majority of the strains which produced lesions in rabbits, when in the primary culture, grew poorly or not at all on blood-agar plates. The tall tubes of glucose-brain agar kept the colonies separated and were therefore a good index of the degree of infection present. The glucose-brain broth furnished the correct oxygen tension for growth, and such cultures were used for animal experiments. In all of the experiments, the rabbits were taken from a common stock used also by investigators in other fields of research without special regard to pedigree as long as they were healthy. Freshly isolated cultures, approximately from eighteen to twenty-four hours old, were inoculated intravenously into the marginal vein of the ear in dosages varying from 2 to 12 cc, depending on the size of the rabbit and the density of the culture. This injection was repeated once or twice with rapidly made subcultures, depending on the condition of the rabbit or the particular purpose of the experiment. For example, repeated injections were given when we wished to produce lesions in various stages of healing. The size of the doses also varied because the production of lesions in animals by injection of streptococci is not a stereotyped and constant occurrence as is the ability of the bacillus of tuberculosis to infect guinea-pigs, the localizing power of strains varies in the rabbits just as it produces inconstant effects in man. Hence the dosage was varied in order that somewhere in that range we might produce all conditions suitable and reproduce in the animal the lesion of the patient. The average length of life of the rabbit was five or six days. The majority of the rabbits were chloroformed. Necropsy was performed as soon as possible after death because of the rapid postmortem changes which occur in the stomach. None of the dogs was chloroformed, but all were allowed to live indefinitely, they were examined as soon as possible after death.

RESULTS

Of the eighty consecutive cases studied, only one failed to reveal a focus at the time of admission. This was a case of primary duodenal ulcer. Septic tonsils and two infected teeth had been removed a few weeks prior to registration because of choroid retinitis. In all of the remaining seventy-nine cases, eighteen of recurring and sixty-one of primary ulcer, one or more foci of infection were found in teeth, tonsils or prostate. The green-producing streptococcus was isolated either in pure or in mixed culture, and when injected intravenously into rabbits, produced hemorrhages, erosions or ulcerations in either the stomach or the duodenum or in both. In the three women in our first series, all the cultures from the cervix were negative or of no consequence.

The prostate was found to be the only apparent focus of infection in ten cases and one of several foci in thirty-one of the seventy-six cases in men. In twenty-three of these the infection in the prostate was clinically graded 1 or 2, while in one case in which the prostate was normal clinically, a culture yielded a pure growth, a green-producing streptococcus which produced lesions when injected into animals. The tonsils or tonsillar tags furnished the only recognizable focus in twenty-nine cases, and in only eleven of these were the tonsils considered septic clinically. The teeth served as the only demonstrable focus in twelve cases. The majority of the teeth from which cultures were taken were devitalized but roentgenologically negative. They were found to be infected, however, as often as were the devitalized roentgenologically-positive teeth, and cultures from their apices often produced more typical lesions of the stomach and duodenum of rabbits than did the cultures of the devitalized, roentgenologically-positive teeth.

One hundred and three strains of green-producing streptococci were obtained from various foci of the 61 cases of primary ulcer, these were injected into 219 rabbits (table 1). Lesions of the stomach or duodenum were obtained in 137 (63 per cent) of the animals injected. In contrast to this, lesions were produced in the gallbladder in only 1 per cent, in the appendix in 8 per cent, in joints in 3 per cent, in the kidneys in 3 per cent and in the heart in 1 per cent. Of the 103 strains of streptococci, 27 were recovered from dental areas of infection, 65 animals were injected with the strains, and lesions of the stomach and duodenum were found in 39 (60 per cent). Forty-nine strains were obtained from tonsils or tonsillar tags, 106 animals were injected with these strains, and similar lesions were found in 76 (72 per cent). Twenty-seven strains recovered from the prostate were injected into 48 animals, and similar lesions were found in 25 (52 per cent). Of the 34 strains obtained from 18 cases of recurring ulcer, 7 were from dental areas of infection, 21 animals were injected with these 7 strains, and

lesions in the stomach or duodenum were obtained in 17 (81 per cent) Fifteen strains were obtained from tonsillar foci and injected into 36 animals, lesions occurred in the stomach or duodenum in 26 (72 per cent) Twelve strains were obtained from the prostate and injected into 19 animals, in 11 of which (58 per cent) lesions were found in the stomach or duodenum Altogether 34 strains of green-producing streptococci were obtained from cases of recurring peptic ulcer, these were injected into 76 animals, and of these 54 (71 per cent) manifested gastric or duodenal lesions In only 2 per cent were there lesions in the gallbladder, in 4 per cent in the appendix, in 4 per cent in the joints, in 5 per cent in the kidney and in 1 per cent in the heart (table 1)

In contrast to these are the control rabbits (table 1) previously reported on by one of us,⁵⁰ which were injected with cultures from foci

TABLE 1—*Experimental Peptic Ulcer*

| Source of Culture | Number of | | | Percentage of Rabbits Having Lesions of the | | | | | |
|------------------------|------------------|------------------|------------------|---|--------------|----------|-------|---------|--------|
| | Strains Cultured | Strains Positive | Rabbits Injected | Primary Ulcer | | | | | |
| | | | | Stomach or duodenum | Gall-bladder | Appendix | Heart | Kidneys | Joints |
| Teeth | 27 | 21 | 65 | 60 | | 5 | | 2 | 5 |
| Tonsils | 49 | 38 | 106 | 72 | 2 | 2 | | 3 | |
| Prostate | 27 | 21 | 48 | 52 | | 10 | 2 | 2 | 2 |
| Total | 103 | 80 | 219 | 63 | 1 | 8 | 1 | 3 | 3 |
| Source of Culture | Number of | | | Recurring Ulcer | | | | | |
| | Strains Cultured | Strains Positive | Rabbits Injected | Stomach or duodenum | Gall-bladder | Appendix | Heart | Kidneys | Joints |
| | | | | Stomach or duodenum | Gall-bladder | Appendix | Heart | Kidneys | Joints |
| Teeth | 7 | 7 | 21 | 81 | 10 | | | 5 | 10 |
| Tonsils | 15 | 13 | 36 | 72 | | 6 | 3 | 8 | 3 |
| Prostate | 12 | 10 | 19 | 58 | | 5 | | | |
| Total | 34 | 30 | 76 | 71 | 2 | 4 | 1 | 5 | 4 |
| Controls (undiagnosed) | 77 | | 190 | 3 | 2 | | 3 | 2 | 7 |

in cases in which no definite diagnosis was made In this group there were lesions of the stomach and duodenum in only 3 per cent of the animals injected, of the heart in 3 per cent, of the joints in 7 per cent and of the gallbladder and kidneys in 2 per cent It is readily seen that there is no marked selectivity of the micro-organisms in the control group for any part of the body, while the strains isolated in cases of peptic ulcer show definite selectivity for the stomach and duodenum

The localizing power of the streptococcus so constantly found in the infective foci in cases of peptic ulcer is further illustrated by the results obtained from another series of 11 cases of peptic ulcer in which operation was performed At operation, gastric ulcer was found in 4 of the 11, duodenal ulcer in 4 and gastrojejunal ulcer in 3 In 10 of these 11 cases, the green-producing streptococcus was isolated from the

50 Nickel, A C The Localization in Animals of Bacteria Isolated from Foci of Infection, J A M A 87 1117 (Oct 2) 1926

resected ulcers, and all 10 strains produced specific lesions in rabbits. In 28 of 31 rabbits injected intravenously with these strains, hemorrhagic erosions or ulcers were found in the stomach or duodenum (table 2). The infective foci in these 11 cases were investigated in the same manner as in our first series. A tonsillar or nasopharyngeal culture was obtained in every case, and in 9 of the 11 injections into experimental animals it produced gastric or duodenal lesions. Of the 22 rabbits injected intravenously with these tonsillar and nasopharyngeal cultures, lesions of the stomach or duodenum were found in 13. Two of 3 cultures obtained from the teeth in these cases produced gastric or duodenal lesions in rabbits, and similar lesions were found in 3 of the 8 rabbits injected with the cultures from the teeth. Similarly, 1 of 6 cultures from the prostate in this series contained streptococci, and a rabbit injected with this cul-

TABLE 2—*Incidence of Lesions in Rabbits Injected with Streptococci Isolated from Operative Cases of Peptic Ulcer*

| Source of Strepto- cocci | Number of Strains | | Number of Animals | | Lesions in | | | | | | | | |
|--|----------------------|---------------------------------------|----------------------|-------------------------------------|----------------------|----------------------|--|----------------------|--------------------|---------------------|-------|-------|--------------|
| | In- jected | Pro- ducing Specific Lesions | In- jected | Show- ing Specific Lesions | Stomach | | Duode- num, Hem- or- rhage | Gall blad- der | Ap- pen- dix | In- tes- tine | Heart | Lungs | Kid- neys |
| | | | | | Hem- or- rhage | Ul- cera- tion | | | | | | | |
| Resected peptic ulcers in man | 10 | 10 | 31 | 28 | 19 | 14 | 6 | | | 1 | | | 2 |
| Tonsils or naso- pharynx | 11 | 9 | 22 | 13 | 10 | 4 | 4 | 2 | | 2 | 1 | 2 | 2 |
| Teeth | 3 | 2 | 8 | 3 | 1 | 1 | 1 | | | | 1 | | |
| Prostate | 1 | 1 | 1 | 1 | 1 | | | | | | | | |
| Total | | | 62 | 45 | 31 | 19 | 11 | 2 | | 3 | 2 | 2 | 4 |
| Percentage localization | | | | 73 | | | | 3 | | 5 | 3 | 3 | 7 |

ture likewise manifested peptic lesions. Thus, of 61 animals injected with cultures from peptic ulcers and infective foci in the cases of this second series, lesions of the stomach or duodenum were found in 45 (73 per cent), in contrast to lesions of the gallbladder, heart and lungs in 3 per cent, of the intestines in 5 per cent and of the kidneys in 7 per cent.

To determine still further the elective localizing power of these organisms, strains freshly isolated from rabbits with definite lesions of the stomach or duodenum were introduced into the pulp chambers of dogs' teeth in the hope of stimulating a chronic dental focus in man. In some of the dogs only the pulps of four teeth were infected, in others gastro-enterostomy also was performed. In both groups of dogs, those that lived only several months manifested submucous hemorrhagic lesions about the gastro-enteric stoma and distal loop of bowel, while in those that lived a year or longer definite chronic

ulcerations tended to form on the lesser curvature of the stomach or in the distal loop of the bowel, in several, perforation occurred. At necropsy a roentgenogram of the infected teeth frequently showed rarefaction at the apex, and the majority of the cultures obtained from the pulp chambers, as long as one and two-thirds years after inoculation, contained the living streptococcus which still maintained its ability to localize electively in the stomach and duodenum of rabbits when injected intravenously.

ILLUSTRATIVE CASES OF PEPTIC ULCER

CASE 1—A Russian Jew, aged 39, entered the Mayo Clinic in June, 1923, with a history of "stomach trouble" for the previous nine years. This distress began



Fig 1 (case 1) —Section through the side wall of a resected gastric ulcer of man showing marked cellular infiltration and necrotic material near the base. Hematoxylin and eosin stain, $\times 25$.

as a dull pain in the epigastrium, at times accompanied by vomiting, and he often complained of flatulency. Definite symptoms of ulcer could not be elicited from the history. In January, 1915, appendectomy gave no relief. Three months later, gastro-enterostomy was performed and five months later, a second gastric operation (nature unknown). The patient was somewhat relieved for two months, he then went on a general diet and soon after began to complain of rather severe pain in the left side of the epigastrium, this pain was relieved by food. However, he suffered from continuous "full-pressure" pain in the same region. He followed the Sippy diet for three years, but was not greatly relieved. He did not vomit and did not have a hemorrhage.

The patient's physical condition was poor. The Wassermann test of the blood was negative. The total gastric acidity was 56 and free hydrochloric acid 42, a roentgenogram of the stomach was normal. Pyorrhea was present (graded 2), and there were four infected roots of teeth. Because of the persistence of the complaints and the presence of an indefinite mass to the left of the navel, an exploratory operation was performed on June 23. The stomach was adherent to the anterior abdominal wall at the site of a previous anastomosis, and at this site there was a perforating ulcer with a crater 1 cm in diameter. The ulcer was excised and the anterior gastro-enteric anastomosis reconstructed. The patient improved after this operation, gained weight and had no gastric complaints for about one year. Because of trouble with the teeth and sore gums, all of the teeth and supposedly the root tips were extracted in August, 1924. The patient had failed, his mouth was sore, and he had lost 10 pounds (4.5 Kg) in weight, which were never regained. He returned to the Mayo Clinic in January, 1926. Ten or eleven months prior to this, the old epigastric pain recurred and was constant except when temporarily relieved by food and alkali, at times it was severe, even when he was on a soft diet. There was a distinct mass to the left of the umbili-

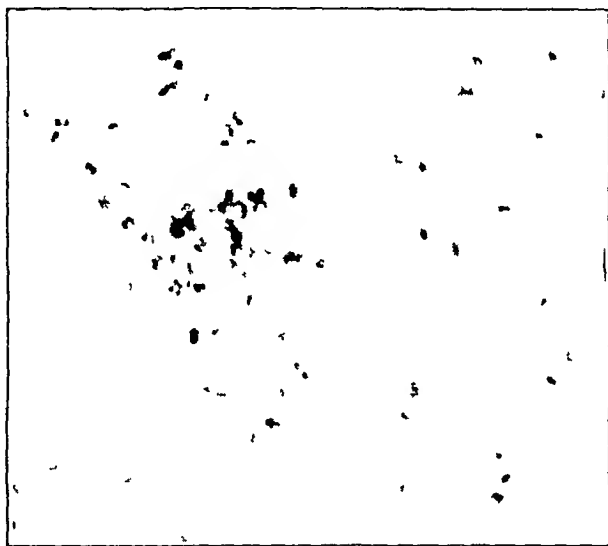


Fig 2—Many diplococci found in the depths of the wall of the ulcer, shown in figure 1. Gram-Weigert stain, $\times 1000$

cus, which was tender. The tonsils were medium-sized and contained soft plugs, the prostate was normal clinically and negative culturally, but there were five remaining tooth root tips. The roentgenogram of the stomach revealed a gastrojejunal ulcer. At operation it was found that the ulcer had recurred in the anterior portion of the stomach and was attached to the anterior abdominal wall in the scar tissue. The ulcer was 4 cm in diameter and 2 cm deep. The anastomosis was separated, the crater in the abdominal wall excised, the jejunum closed and the pyloric two thirds of the stomach resected. Section of the ulcer stained by the Gram stain revealed the diplococcus deep in the inflammatory tissues. The root tips were removed. In two of the four animals injected with the cultures, duodenal lesions were found. Cultures of the tonsils consisted of almost pure green-producing streptococci. The three rabbits injected with the culture from the tonsils manifested gastric or duodenal lesions.

The patient was free from symptoms on dismissal from the clinic. One year later, he returned for reexamination. He said that he had not any gastric distress.

CASE 2—A man, aged 31, said that he had had periodic gastric distress since 1918, which he described as a gnawing pain two or three hours after meals, accompanied at times by tarry stools and flatulency and vomiting when he had eaten a heavy meal. Two courses of medical treatment in the hospital relieved the symptoms for a few months. For two months prior to coming to the Mayo Clinic, he had suffered from gastric distress and vomiting daily.

On examination, considerable tenderness was found in the midepigastrium. The systolic blood pressure was 120 and the diastolic 85. Total gastric acidity was 40 and free hydrochloric acid 20. A roentgenogram of the stomach revealed a perforating ulcer on the lesser curvature. At operation, two large perforating gastric ulcers were found near the lesser curvature, with considerable inflammatory reaction (fig 1). Partial gastric resection, Billroth II, and appendectomy were performed.

In cultures made from emulsions of a portion of the resected ulcer there were green-producing streptococci, streptococci were also found in sections of the resected ulcer (fig 2). All of the rabbits injected with this primary culture



Fig 3—Diffuse submucous hemorrhages in the first portion of the duodenum of a rabbit injected several times with a freshly isolated culture from the tonsil of a patient having peptic ulcer. Note also the hemorrhagic ulceration of the fundus, $\times 1$.

manifested gastroduodenal lesions. Similar lesions were found in rabbits after they had been injected with cultures (from the patient's ulcer) passed once and twice through animals. In cultures from the patient's tonsils green-producing streptococci were found, which also produced hemorrhagic erosions when injected into two animals.

PATHOLOGIC OBSERVATIONS

The predominating causative organism in all of these experiments was found to be a green-producing streptococcus. Morphologically and according to sugar reactions, it was often indistinguishable from other green-producing strains of streptococci which were isolated in cases of arthritis, myositis and other conditions. However, when injected intravenously into rabbits and when inoculated into the teeth of dogs, it had

a marked tendency to localize in the stomach and duodenum instead of in the muscles, nerves or joints. In primary culture it grew poorly or not at all on a blood-agar plate, but it grew readily in partial-tension mediums, such as Rosenow's glucose-brain broth. The lesions produced by the streptococci were chiefly in the duodenum or pyloric portion of



Fig 4—Blood-distended villi, with loss of glandular structure, of the hemorrhagic portion of the duodenum shown in figure 3. Hematoxylin and eosin stain, $\times 120$.



Fig 5—Diplococci scattered through all layers of the duodenum and practically occluding some of the smaller blood vessels beneath the hemorrhages of the duodenum shown in figure 3. Gram-Weigert stain, $\times 1000$.

the stomach and sometimes in the fundus. When in the fundus they tended to heal rapidly, while in the pylorus and duodenum, the healing was slower; in this respect, the ulcers resembled those found in man. In rabbits which had received repeated injections, necropsy often

revealed lesions in various stages of healing, which seemed to indicate a relationship between the lesions and the injected material (fig 3) The lesions of the stomach and duodenum both in rabbits and in dogs resembled those induced by Rosenow and Meisser They consisted of submucous petechial hemorrhages, definite erosions with a hemorrhagic center and well-formed ulcers, often associated with free blood in the lumen The petechial hemorrhages were generally superficial and multiple, and were widely disseminated in the stomach, but when they occurred in the duodenum, they were almost always confined to its first portion between the pylorus and ampulla In advanced conditions, the hemorrhagic areas were often confluent and the glandular structure could hardly be differentiated (figs 3 and 4) These hemorrhages were sometimes beneath the muscularis but more often nearer the surface of

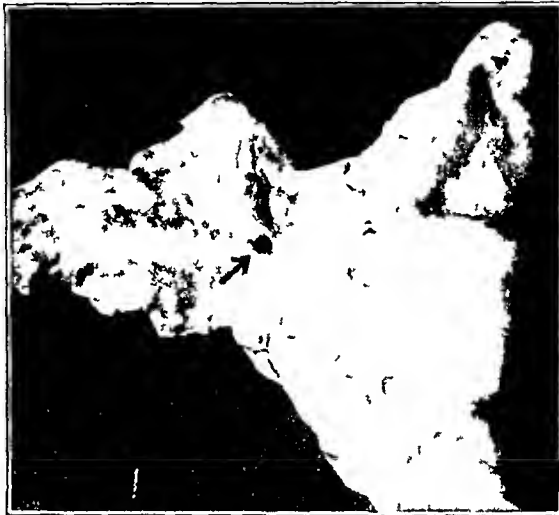


Fig 6—A solitary duodenal ulcer on the posterior wall of the duodenum of a rabbit injected with a tonsillar culture on three successive days The rabbit was chloroformed on the fourth day, $\times 1$

the mucosa, frequently the villi were so distended with blood and fluid that the content of the villus ruptured through the mucosa into the lumen of the stomach or duodenum The amount of cellular infiltration varied but was never extensive The bacteria were usually numerous, and sometimes were clumped inside the vessel wall almost occluding the lumen (fig 5) In other instances, many such hemorrhagic areas were found, some of which had sloughed away, leaving definite erosions or ulcers with a base which sometimes consisted of submucosa or even of muscle, and which was covered with varying amounts of necrotic material (figs 6 and 7) In these cases there was edema throughout the tissues The nuclei of the surrounding cells were indistinct and stained poorly, and there was definite round-cell infiltration which often

extended down into the muscularis. Streptococci were often found mixed with equal numbers of other micro-organisms in the superficial necrotic layers. However, in the depths of the mucosa and submucosa and beneath the necrotic material, these other micro-organisms were not visible, here the streptococci were usually found in pairs near the smaller blood vessels (fig 8), frequently beneath the muscularis and, in perforating cases, near the serosa.

COMMENT

Our results agree favorably with those reported previously by Rosenow and his co-workers and those of Haden and Bohan. If the



Fig 7—Section through an ulcer of the duodenum of a rabbit. Note the marked necrosis with loss of tissue, scattered debris, and the marked cellular infiltration. Hematoxylin and eosin stain, $\times 60$.

results obtained are, as they seem to be, a fair cross-section of all cases of ulcer, they show that the overwhelming number of patients suffering from peptic ulcer harbor such septic foci. In all but one of all cases of ulcer examined, there was one or more definite infective focus in the body at the time the patient registered, from these, streptococci were isolated that produced lesions in the stomach or duodenum of rabbits when injected intravenously. On the other hand, in only comparatively few instances were micro-organisms cultured from infective foci in cases other than those of peptic ulcer localized in the stomach and duo-

denum, when they did localize there, the lesions were fewer in number and were not nearly as pronounced

That the appendix, gallbladder, colon, sinuses or bronchi may also become foci of infection for the streptococcus of the ulcer-producing type is possible, especially if the ulcer persists after other foci have been eradicated. However, our study does not include these foci, because they are generally secondary to some other focus. The foci we did study often looked innocent and were clinically mild, and it was impossible to determine by perception, palpation or roentgen-ray examination which focus harbored the ulcer-producing organism. Mere objective clinical examination of a supposed focus is of little importance in determining which organism a focus contains. No one is able to tell definitely



Fig 8—Diplococci scattered in the submucosa adjacent to the smaller blood vessels near the muscularis mucosa of the ulceration shown in figure 7. Gram-Weigert stain, $\times 1000$

from the appearance of a tonsil, the roentgenogram of a devitalized tooth or the palpation of a prostate what kind of organisms are harbored therein or to state their biologic characteristics. An actual culture is the best known method for determining these facts, even by this method buried tonsil tags, root tips or residual areas in edentulous mouths are overlooked unless watched for carefully, because the local clinical symptoms are generally absent or mild.

In order to evaluate the usual surgical and medical treatment when combined with removal of infective foci and sometimes the use of an autogenous vaccine a questionnaire was sent to eighty of our patients from seven to twelve months after their dismissal from the hospital in

order to ascertain their general health, the presence or absence of digestive distress and their cooperation in the eradication of any remaining foci of infection. Fifty-three replies were received and tabulated. Although generalizations cannot be deduced from such a comparatively small series, there are some results that deserve consideration.

In the cases in which medical treatment was carried out, the ulcers were acute or bleeding, while in the cases in which operation was performed, the ulcers were of a more chronic type. There was practically as much improvement following medical management as following major operations. In the group of thirty-seven cases in which all known foci of infection had been eradicated, the general health had improved, twenty-nine patients reported themselves as well and eight as in fairly good health with some gastric distress at times. There were eight patients treated either medically or surgically, only part of whose infective foci had been eradicated, at the time of the questionnaire, two of these patients were well, five were in fair health and one was unimproved. Of the eight patients who received either surgical or medical treatment but did not cooperate with our request to have evident infective foci removed, only one was well, three were in fairly good health and four stated that they were unimproved. Thus in the majority of cases of peptic ulcer, there were definite foci of infection which contained streptococci having definite affinity for the stomach and duodenum, in the majority of cases in which such foci were eradicated, the patient was well and free from symptoms from seven to twelve months later.

Autogenous vaccine was given to seven patients. One of the seven was not benefited by it after using it for several months, he, however, had neglected to have septic tonsils removed. Of the remaining six, the septic tonsils of one were removed only two months before this article was written, and he is in fairly good condition, the other five are enjoying good health.

SUMMARY AND CONCLUSIONS

1. Foci of infection bear a definite etiologic relationship to primary and recurring peptic ulcers, they are found in almost every case of peptic ulcer, and they have been shown to contain the causative streptococcus.

2. The favorable results obtained by the removal of foci of infection in some cases of peptic ulcers which recurred repeatedly after surgical management indicate that this procedure will help to prevent recurrence.

3. The foci in the teeth, tonsils and prostate which were studied were often obscure and innocent-looking and generally did not produce local symptoms.

4 Devitalized, roentgenologically-negative teeth, act as a focus of infection as often as roentgenologically-positive teeth, according to our experimental results

5 The causative streptococcus has been demonstrated in and isolated from the resected ulcer of man as well as from the foci of infection and has produced, electively, similar lesions of the stomach and duodenum when injected intravenously into rabbits

6 The streptococcus which we have isolated consistently in these cases is identical with that first described by Rosenow as having etiologic importance in the production of peptic ulcer in man, and it provides a means for active immunization with specific autogenous vaccine

SUBLINGUAL ABSORPTION OF DRUGS MORPHINE

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Paulson,¹ being impressed by the accessibility, the thin mucous membrane and the abundant blood supply of the sublingual space, was one of the first to recommend the sublingual administration of drugs. His experience led him to believe that drugs were rapidly absorbed when administered in this manner. Other clinicians have held the same view, and recently Fantus² has advocated the use of this method. But what evidence is there that drugs are readily absorbed from this space?

As far as we know, quantitative studies to determine the selective absorption capacity of this membrane have not been made. The claims found in the literature are, for the most part, based on clinical impressions. It is known that the effects of certain drugs are manifest soon

Quantity of Drug Recovered After Sublingual Administration

| Experiment Number | Quantity of Drug, Mg | Time for Absorption, Minutes | Amount Recovered, Mg | Per Cent Recovered |
|-------------------|----------------------|------------------------------|----------------------|--------------------|
| 1 | 15 | 5 | 13.5 | 90 |
| 2 | 15 | 10 | 9.9 | 66 |
| 3 | 10 | 10 | 6.5 | 65 |
| 4 | 10 | 10 | 8.1 | 81 |
| 5 | 10 | 10 | 7.0 | 70 |
| 6 | 10 | 10 | 7.0 | 70 |
| 7 | 10 | 10 | 7.5 | 75 |

after their sublingual administration, at times, for example, the effects of nitroglycerine seem to appear within a few seconds after its introduction. Atropine and morphine, given the same way, usually act after a few minutes. In such instances, it is difficult to say how the drug entered the circulation. Seconds of distaste seem long to the patient, and the saliva with the drug is often swallowed soon after the drug is administered. The favorable effects are then due to intestinal absorption, and these may appear early with certain drugs.

Bachem,³ Mendel,⁴ Tracy⁵ and others have claimed selective absorption properties for the sublingual and oral mucous membranes, but they

1 Paulson, W. Sublingual Medication, Practitioner **97** 389 (Oct.) 1916
2 Fantus, B. The Technic of Medication, J. A. M. A. **87** 32-33, (July 3) 1926
3 Bachem. Resorption von Arzneimitteln in der Mundhohle, Klin. Wchnschr. **3** 461 (March 11) 1924
4 Mendel, F. Die perlinguale Application der Medikamente, Munchen med. Wchnschr. **69** 1593 (Nov. 17) 1922
5 Tracy, E. A. A Bit of Hormonology, with Practical Applications, Medicine and Surgery, January, 1918, p. 38

have not offered sufficient evidence. Conclusions were drawn from clinical impressions and unsatisfactory experiments. The need for more definite information in a subject of practical importance suggested the present investigation. The study was conducted as follows. A known amount of drug was placed beneath the tongue in the sublingual space, and after a given length of time, the contents were washed out and studied quantitatively to determine the exact amount of drug unabsorbed. This test is simple and gives definite information.

We used this technic in making studies with morphine sulphate. The results show that morphine sulphate in the form ordinarily administered is not appreciably absorbed by the sublingual mucous membrane. In seven experiments in which quantities of 10 and 15 mg. of powdered morphine sulphate were placed under the tongue for periods of five and ten minutes, from 65 to 90 per cent of the drug was recovered. Allowing for loss both in recovery from the mouth and in the determination, we would estimate that probably less than 10 per cent, if any at all, of the total drug was absorbed.

TECHNIC AND METHOD

The quantitative determination of morphine was made according to the method outlined by Gauss,⁶ which employs the Marquis reagent⁷ for the quantitative estimation by means of a colorimeter. This reagent is prepared by adding one part of formaldehyde, U. S. P., to 20 parts of concentrated sulphuric acid. When added to the smallest perceptible amount of pure dry morphine, it immediately gives an intense purplish blue color. This delicacy makes it well suited for quantitative use. When the morphine is nearly pure, extraction is unnecessary, and a direct determination can be made, as follows. Prepare a standard by evaporating an aqueous solution containing exactly 1 mg. of morphine sulphate to dryness. In the same way, prepare the unknown in approximately 1 mg. amounts. To each evaporating dish pipet 10 cc. of freshly prepared Marquis' reagent, and thoroughly mix the coloring by scraping the morphine from the sides of the dish with a glass rod. Match the unknown against the standard in a Dubosq colorimeter.

Impurities, particularly coloring matter, necessitate preliminary extraction, which is accomplished with trichloroacetic acid and chloroform.⁸ In this way, a high percentage of the alkaloid can be recovered, the amount depending on the quantity of morphine present, and the amount and character of the material from which it is extracted.⁸

6 Gauss, H. Colorimetric Method for Estimation of Morphine in Colloidal Mixtures and Tissues, *J. Lab. Clin. Med.* 6:699, 1920-1921.

7 Marquis, Eduard. *Arch. des Pharm. Inst.*, Dorpat, 1896, no. 14, p. 117.

8 Hatcher, R. A., and Davis, D. The Excretion of Morphine Into the Stomach, *J. Pharmacol. & Exper. Therap.*, August, 1925, no. 1, vol. 26.

The saliva collected in each experiment varied from 1 to 5 cc, and as only one fifth or one tenth of this was used for a determination, the impurities were too small appreciably to affect a direct estimation. Less than 0.5 cc of pure saliva usually lowers the reading of 1 mg of pure morphine sulphate by 0.1 mg (10 per cent). This amount of saliva usually produces a slight greenish tinge to the blue coloration, but intensities are easily matched, and in some experiments the colors were almost exact. Equivalent amounts of pure saliva were added to each standard, as a control. It was then unnecessary to extract with chloroform, which, in itself, would entail some loss.

The subjects for these experiments possessed clean mouths and healthy gums. Before each determination, the teeth were brushed and the mouth rinsed with distilled water. An exact quantity of morphine sulphate was placed in the sublingual space, and after an interval of five or ten minutes, the contents were drooled into a receptacle and the mouth rinsed with a known amount of water which was added to the original contents. A small loss is unavoidable as some saliva is swallowed.

CONCLUSIONS

- 1 The absorption capacity of the sublingual mucous membrane was studied by introducing a known amount of morphine sulphate beneath the tongue, and later analyzing the contents of the mouth to determine the exact amount of drug unabsorbed.

- 2 The results of these studies show that morphine sulphate, in the form ordinarily administered, is not appreciably absorbed by the sublingual mucous membrane.

- 3 A review of the meager literature on this subject failed to reveal sufficient evidence to support the notion that the sublingual mucous membrane has the capacity to absorb drugs rapidly. On the contrary, the results with morphine sulphate, which is readily soluble in water and quickly absorbed from gastro-intestinal and rectal mucous membranes, suggest that allied drugs are also little absorbed by the sublingual membrane.

- 4 The sublingual administration of morphine should be discontinued.

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CHEMICAL CHANGES IN THE BLOOD IN MERCURIC CHLORIDE POISONING

MECHANISM AND SIGNIFICANCE OF HYPOCHLOREMIA *

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A marked reduction of the blood chlorides may occur in any patient suffering from mercury poisoning. In his fatal cases of poisoning with mercuric chloride, Heim¹ observed a lower concentration of blood chlorides than in any other condition, the lowest figure being 210 mg sodium chloride per hundred cubic centimeters of blood. In his discussion of theories to explain the condition, he concluded that the hypochloremia could not be explained by a loss of chlorides from the intestinal tract either by vomiting or by diarrhea. As an alternate possibility, he offered the view that a specific poisoning of vascular membranes or a physiochemical change in the blood permits a loss of sodium chloride directly into the tissues.

Data in proof of either theory have not been offered, and we feel that a metabolic change of such fundamental importance merits experimental investigation. With this point in view, we have studied the chemical changes in the blood of dogs and rabbits following the intravenous injection of mercuric chloride.

EXPERIMENTS

In the course of these studies, twenty-two dogs and seven rabbits were killed. A stock solution of mercuric chloride, 1 per cent in distilled water, was prepared for intravenous injection. The size and number of doses were varied sufficiently to give a complete check on results. All injections were given carefully and slowly to prevent circulatory accidents and to avoid the confusion of sudden or unusual toxic effects. The several protocols and tables, selected for detailed study, demonstrate

* From the Department of Surgical Pathology, Indiana University School of Medicine, the Eli Lilly Research Fellowship.

* This experimental work was made possible through the courtesy of Dr W D Gatch.

* The chemical analyses were done in the department of Biochemistry under the supervision of Dr B B Turner and Dr R N Harger.

1 Heim, F. Hypochloremia in Poisoning with Mercuric Chloride, *Schweiz med Wchnschr* 55 1085 (Nov 26) 1925.

the results consistently obtained in each series of experiments. Further reduplication of data is considered unnecessary.

TOXICITY OF MERCURIC CHLORIDE INJECTED INTRAVENOUSLY INTO DOGS

Dogs showed marked variation in their individual reaction to mercury poisoning by this method. Our experiments have shown that a single intravenous dose of 1 mg of mercuric chloride per kilogram of body weight may not produce any significant change in the normal dog. However, a dog of reduced vitality may develop a violent intoxication and die within a week following such an injection. A dose of 4 mg per kilogram is uniformly fatal in about three days' time. Injections of 2 and 3 mg per kilogram are fatal after an interval which may vary from six days to six weeks. Repeated small injections are similarly fatal. The various changes which occur are considered in detail throughout the following discussion.

TABLE 1—*Results of Intravenous Injection of Mercuric Chloride into Dog 1**

| Day | Mg per 100 Cc of Blood | | |
|-----|------------------------|---------------|---------------------------|
| | Sodium Chloride | Urea Nitrogen | Total Nonprotein Nitrogen |
| 0 | 470.3 | 15.2 | 36.0 |
| 2 | 437.3 | | 37.5 |
| 20 | 456.0 | 33.1 | 88.2 |
| 38 | 461.0 | 20.2 | 48.0 |

* No significant changes followed a single intravenous injection of 1 mg of mercuric chloride per kilogram of body weight.

SUBACUTE MERCURIAL POISONING

In the slowly developing intoxication which ordinarily follows the smaller injections of mercury, only a gradual reduction in the function of the kidney is observed, as shown by the slow accumulation of nitrogenous elements in the blood. Vomiting and marked diarrhea do not occur, nor a significant change in the blood chlorides. There is salivation, loss of appetite, loss of weight and lethargy, from which state the animal may recover or may lapse into a fatal coma.

Dog 1 (table 1)—A vigorous animal, weighing 22 Kg, received by intravenous injection 22 cc of 1 per cent solution of mercuric chloride (1 mg per kilogram). With the exception of slight diarrhea and mild salivation in the first few days, the animal appeared normal. There was a temporary reduction in weight, but after six weeks the dog appeared to have entirely recovered.

Dog 2—A healthy young animal weighing 10 Kg received injections of mercuric chloride as indicated in table 2. The dog was penned in a metabolism cage and allowed as much water as he wanted but no food. Excretions were analyzed to determine sodium chloride output. The animal appeared essentially normal for fourteen days, during which time he had received five injections of 0.6 mg mercuric chloride per kilogram and two injections of 1.25 mg per kilo-

gram On the nineteenth day, however, following an injection of 25 mg per kilogram, he lapsed into coma and died on the twenty-first day Histologic examination of the kidneys showed the early changes of acute tubular nephritis

From a study of the first two protocols and tables, it will be noted that dog 1, following a single intravenous injection of 1 mg mercuric chloride per kilogram, showed only a temporary slight increase in the nitrogenous elements of the blood He did not vomit, and there was no change in the blood chlorides Likewise, dog 2 endured seven small injections of mercuric chloride over a period of two weeks During this time the chemical changes in the blood were only those of starvation The sodium chloride excretions in the urine were those of a starving animal, vomiting did not occur, and there were no changes in the blood chlorides On the seventeenth day, however, he received an intravenous injection of 25 mg mercuric chloride per kilogram In the twenty-four

TABLE 2—*Result of Intravenous Injections of Mercuric Chloride Into Dog 2**

| Day | Intravenous Injections of Mercuric Chloride, Mg per Kg of Body Weight | Mg per 100 Cc of Blood | | | Urine | | Vomit | |
|-----|---|------------------------|---------------|---------------------------|------------|---------------------|------------|---------------------|
| | | Sodium Chloride | Urea Nitrogen | Total Nonprotein Nitrogen | Volume, Cc | Sodium Chloride, Gm | Volume, Cc | Sodium Chloride, Gm |
| 0 | 0.6 | 459 | 20.5 | 43.8 | | | | |
| 3 | 0.6 | 459 | 13.4 | 40.0 | 1,350 | 2.9 | None | |
| 5 | 0.6 | 450 | 12.2 | 36.6 | | | | |
| 7 | 0.6 | 458 | 10.6 | 28.6 | 700 | 1.1 | None | |
| 9 | 0.6 | 435 | 11.6 | 26.4 | | | | |
| 12 | 1.25 | 440 | 9.8 | 33.7 | 560 | 0.7 | None | |
| 14 | 1.25 | 462 | 6.2 | 31.9 | 90 | 0.2 | None | |
| 17 | 2.5 | 462 | 10.2 | 32.5 | 180 | 0.4 | None | |
| 18 | None | 440 | 34.8 | 65.0 | None | | 500 | 2.7 |
| 19 | None | 372 | 43.6 | 98.3 | None | | None | |
| 21 | At death | 429 | 191.6 | 339.6 | None | | None | 2.5† |

* Multiple small injections of mercuric chloride were given intravenously

† Washings from pen

hours which followed there was 500 cc of vomitus, the titration of which yielded 2.7 Gm of sodium chloride The additional 2.5 Gm recovered in the final washing of the pen must also have been chiefly the result of this vomiting Accompanying this, there was a sharp reduction in the blood chlorides Further losses of chloride did not occur, and the sodium chloride content of the blood again rose, conceivably owing to absorption from the tissues In addition to this change, the terminal blood showed the nitrogen accumulation of complete urinary suppression

ACUTE MERCURIAL POISONING

Acute rapidly fatal mercurial poisoning is characterized by a sudden suppression of urine, a rapid accumulation of nitrogenous elements in the blood, and acidosis as shown by a marked reduction of the carbon dioxide combined in the plasma and violent intoxication Accompanying this, there was an excessive loss of chlorides through vomiting and a marked reduction in the sodium chloride of the blood

Dog 17 (table 3)—During the previous three months, this animal had been subjected to deep ether anesthesia on three occasions for experimental study. Finally, the gallbladder was removed. He appeared normal, well nourished and healthy. As he weighed 19 Kg, he received a single intravenous injection containing 19 mg of mercuric chloride (1 mg per kilogram). His reaction was the violent intoxication characteristic of a much larger dose. He was dead at the end of six days.

Dog 3 (table 4)—A healthy animal weighing 16 Kg received four intravenous injections of 20 mg of mercuric chloride at forty-eight hour intervals. This dog was penned in a metabolism cage and allowed as much water as he wanted but no food. There was a sharp terminal reduction in the sodium chloride of the blood immediately following an excessive loss of chlorides by vomiting.

TABLE 3—*Unusual Reaction of Dog 17 to the Intravenous Injection of Mercuric Chloride*

| Day | Mg per 100 Cc of Blood | | | Output in Vomitus, No Urine | |
|----------|------------------------|---------------|---------------------------|-----------------------------|---------------------|
| | Sodium Chloride | Urea Nitrogen | Total Nonprotein Nitrogen | Volume | Sodium Chloride, Gm |
| 0 | 481 | 31.2 | 41.9 | | |
| 3 | 337 | 117.6 | 170.1 | 1,300 | 7.5 |
| 6 | 271 | 203.6 | 403.6 | 730 | 4.1 |
| At death | | | | | |

TABLE 4—*Marked Reduction of Blood Chlorides Following an Attack of Excessive Vomiting as a Result of Intravenous Injection of Mercuric Chloride Into Dog 3*

| Day | Intravenous Injections of Mercuric Chloride, Mg per Kg | Mg per 100 Cc of Blood | | | Carbon Dioxide Combined in 100 Cc of Plasma | Urine | | Vomitus | |
|-----|--|------------------------|---------------|---------------------------|---|------------|---------------------|------------|---------------------|
| | | Sodium Chloride | Urea Nitrogen | Total Nonprotein Nitrogen | | Volume, Cc | Sodium Chloride, Gm | Volume, Cc | Sodium Chloride, Gm |
| 0 | 1.25 | 459 | 14.0 | 39.0 | 51 cc | | | | |
| 2 | 1.25 | 470 | 78.9 | 130.5 | 36 cc | 1,200 | 2.5 | None | None |
| 4 | 1.25 | 435 | 157.2 | 226.4 | 27 cc | 400 | 0.5 | None | None |
| 6 | 1.25 | 412 | 230.4 | 449.8 | | None | None | None | None |
| 8 | At death | 183 | 334.4 | 555.0 | 36 cc | None | None | 1,010 | 7.8 |

Necropsy on the eighth day showed a marked destruction of the renal tubules and necrosis of the liver. In the last two days of life, tetany was a marked symptom.

Dog 9 (table 5)—An intravenous injection was given of 25 mg of mercuric chloride per kilogram. The dog was penned in a metabolism cage for the collection of sodium chloride excretion, allowed as much water as he wanted but no other food. A reduction of blood chlorides followed an excessive loss of sodium chloride by vomiting in the last four days. The dog died of tetany. Analysis of the liver and muscle showed a reduction of the sodium chloride in these tissues. Necropsy on the eighth day showed cloudy swelling in the parenchymatous tissues and the typical necrosis of renal tubules.

Dog 6 (table 6)—One intravenous injection of 4 mg of mercuric chloride per kilogram. The typical rapidly fatal intoxication followed. Necropsy on the third day showed total destruction of the convoluted tubules in the kidney and acute parenchymatous degeneration in all other tissues. The chloride losses are indicated in the table.

An analysis of the foregoing protocols and tables reveals three main factors contributing to the fatal course of mercuric chloride poisoning

1 Following a massive dose of the poison, a generalized intoxication is rapidly fatal. The chemical changes which occur in the blood during this interval are insufficient to account for the early death. The fatal mechanism in this case must be direct injury to vital centers.

2 Following doses of less toxicity, the chief damage occurs in the convoluted tubules of the kidney. Other things remaining equal, the rapidity of the fatal course is proportional to the reduction of renal function which results from this damage to the kidney.

TABLE 5—Results of Intravenous Injection of 2.5 Mg of Mercuric Chloride Per Kilogram Into Dog 9

| Day | Mg per 100 Cc of Blood | | | Urine | | Vomit | |
|----------|------------------------|---------------|---------------------------|------------|---------------------|------------|---------------------|
| | Sodium Chloride | Urea Nitrogen | Total Nonprotein Nitrogen | Volume, Cc | Sodium Chloride, Gm | Volume, Cc | Sodium Chloride, Gm |
| 0 | 479 | 33.0 | 61.2 | | | | |
| 2 | 524 | 53.2 | 89.8 | 200 | 0.5 | 800 | 3.0 |
| 4 | 506 | 108.0 | 154.6 | 160 | 0.1 | 270 | 1.2 |
| 8 | 287 | 430.6 | 600.1 | None | None | 1,470 | 12.1 |
| At death | | | | | | | |

Sodium chloride in tissues: liver, 1.4 Gm per Kg; muscle, 0.73 Gm per Kg.

TABLE 6—Result of Intravenous Injection Into Dog 6, Followed by Fatal Intoxication on the Third Day

| Day | Mg per 100 Cc of Blood | | | Carbon Dioxide Combined in 100 Cc Plasma | Urine | Vomit | |
|----------|------------------------|---------------|---------------------------|--|-------|------------|---------------------|
| | Sodium Chloride | Urea Nitrogen | Total Nonprotein Nitrogen | | | Volume, Cc | Sodium Chloride, Gm |
| 0 | 543 | 24.0 | 48.0 | 52 cc | | | |
| 2 | 384 | 107.0 | 170.0 | 33 cc | None | 980 | 8.0 |
| 3 | 316 | 143.2 | 181.8 | 24 cc | None | 200 | 2.4 |
| At death | | | | | | | |

* One intravenous injection containing 4 mg mercuric chloride per kilogram.

3 There is a severe gastro-intestinal irritation which in dogs results in excessive losses of chlorides through vomiting. Accompanying this loss there is a reduction in the sodium chloride in the blood. The gastric tetany which results may of itself be fatal. In these experiments we have never observed a marked reduction of the sodium chloride in the blood which was not explained by losses of chloride from vomiting.

Our experiments with rabbits supply additional evidence of this relationship. As the rabbit is an animal that does not vomit, avenues for excessive loss of chloride from the body are not found. It is significant that acute mercury poisoning in rabbits is not accompanied by any marked reduction in the sodium chloride of the blood.

In these studies of animals it has been evident that the reduction of blood chlorides results directly from loss of chloride through vomiting, and not from any obscure toxic change in the blood or its vessels. This view is in keeping with the conclusions set forth in a previous publication² concerning the hypochloremia of acute intestinal obstruction.

SIGNIFICANCE OF HYPOCHLOREMIA IN MERCURY POISONING

The vomiting which we have observed in these dogs results not only from gastro-intestinal irritation by the poison, but also as a symptom of

TABLE 7—Results of Intravenous Injection of 3 Mg of Mercuric Chloride Per Kilogram Into Three Rabbits

| Rabbit Number | Day | Mg per 100 Cc of Blood | |
|---------------|------------|------------------------|---------------------------|
| | | Sodium Chloride | Total Nonprotein Nitrogen |
| 4 | 0 | 445.5 | 33.9 |
| | 3 | 435.0 | 385.4 |
| | 4 at death | 478.0 | 454.5 |
| 5 | 0 | 463.6 | 41.6 |
| | 3 | 435.6 | 315.6 |
| | 4 at death | 495.0 | 438.0 |
| 7 | 0 | 453.7 | 47.6 |
| | 3 | 417.4 | 220.5 |
| | 4 | 445.5 | 265.5 |

TABLE 8—Results of Intravenous Injections of 4 Mg of Mercuric Chloride Per Kilogram and Hypodermic Injection of Salt Solution

| Day | Comment | Mg per 100 Cc of Blood | | | Carbon Dioxide Combined in 100 Cc Plasma | Urine | | Vomit | |
|-----|---|------------------------|---------------|----------------------------|--|------------|---------------------|------------|---------------------|
| | | Sodium Chloride | Urea Nitrogen | Total Non-protein Nitrogen | | Volume, Cc | Sodium Chloride, Gm | Volume, Cc | Sodium Chloride, Gm |
| 0 | | 486.7 | 23.0 | 45.5 | | | | | |
| 1 | | 389.1 | 35.6 | 86.1 | 48 cc | 370 | 1.3 | 360 | 4.6 |
| 3 | Dog in severe tetany relieved by 1,000 cc 1% sodium chloride hypodermically | 305.0 | 155.0 | 263.5 | 21.1 cc | None | None | 700 | 4.3 |
| 4 | 500 cc 1% sodium chloride | 412.0 | 167.0 | 234.0 | | None | None | None | None |
| 5 | Dog dying | 495.0 | 262.0 | 410.0 | 26.8 cc | None | None | 590 | 6.0 |

urinary suppression. As the senior author² has previously shown, dogs vomit excessively following the removal of both kidneys or ligation of both ureters. The significance of the reduction in blood chlorides will be considered in detail.

Dog 5 (table 8).—Dog 5 received intravenous injections of 4 mg of mercuric chloride per kilogram. At the end of three days, he was dying in a state of tetany. This symptom was relieved entirely by hypodermic administration of

2 Gatch, W. D., Trusler, H. M., and Ayres, K. D. Acute Intestinal Obstruction: Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes, *Am J M Sc* **173**: 649 (May) 1927.

1,000 cc of 1 per cent sodium chloride. There was a marked temporary improvement. The animal lived for two more days. The blood chloride remained normal, and tetany did not return. Necropsy on the fifth day showed the typical changes of mercury poisoning.

This experiment brings out one point which we wish to emphasize strongly. In the past, many have held the view that gastric tetany is always associated with a state of alkalosis, as shown by an increase in the carbon dioxide combined in the plasma. In dogs with mercury poisoning, the blood invariably shows a state of acidosis. Nevertheless, these animals all exhibit marked tetany as the sodium chloride in the blood falls below 300 mg per hundred cubic centimeters. As is shown in table 8, the tetany is relieved at once by restoration of the blood chloride level.

TABLE 9—*Results of Intravenous Injections of 4 Mg of Mercuric Chloride Per Kilogram Into Dog 7, Sodium Chloride was Also Administered*

| Day | Intravenous Injections of 2% Sodium Chloride, Cc | Mg per 100 Cc of Blood | | | Urine | | Vomitus | |
|-----|--|------------------------|------------------|---------------------------------|---------------|---------------------------|---------------|---------------------------|
| | | Sodium Chloride | Urea Nitrogen | Total Nonprotein Nitrogen | Volume, Cc | Sodium Chloride, Gm | Volume, Cc | Sodium Chloride, Gm |
| 0 | 500 | 525 | 30.1 | 57.0 | | | | |
| 1 | 500 | 427 | 60.5 | 111.0 | 480 | 2.0 | 2,280 | 14.5 |
| 2 | 500 | 506 | 101.2 | 159.4 | 370 | 0.7 | 2,160 | 5.2 |
| 3 | 500 | 552 | 120.6 | 166.6 | 70 | 0.4 | 1,960 | 6.4 |
| 4 | 500 | 570 | 131.8 | 180.7 | 130 | 0.7 | 830 | 4.2 |
| 5 | 500 | 551 | 193.2 | 182.8 | 100 | 0.7 | 1,560 | 5.1 |
| 7 | None | 448 | 224.0 | 225.0 | None | None | 2,430 | 7.9 |
| 8 | At death | 472 | 230.0 | 306.0 | None | None | 1,600 | 9.0 |

Liver, 25 Gm sodium chloride per Kg, muscle, 13 Gm sodium chloride per Kg

We conclude, therefore, that gastric tetany is a symptom of hypochloremia without direct relationship to the concentration of the carbonate buffer substances in the blood.

The hypochloremia is easily relieved or prevented by the administration of sodium chloride solution. The accompanying protocols and tables demonstrate, however, that this measure is of secondary importance in mercury poisoning.

Dog 7 (table 9)—Dog 7 received 4 mg of mercuric chloride per kilogram, together with 500 cc of 2 per cent salt solution intravenously. During the next five days, he received five more intravenous injections of 500 cc of 2 per cent salt solution. He lived eight days. Necropsy showed the typical changes of severe mercury poisoning.

As shown in table 10, dog 14 received intravenously a sufficient amount of 1 per cent salt solution to maintain a safe level of blood chlorides, but he was not benefited thereby. His course was practically the same as that of dog 15, which did not receive any treatment. These animals received 2 mg of mercuric chloride per kilogram and lived seven and six days, respectively. Dog 7, table 9, received 4 mg of mercuric

chloride per kilogram (a dose uniformly fatal in the untreated animal in three days) In the first five days, however, this dog received six intravenous injections of 500 cc of 2 per cent sodium chloride solution By far the greater part of this salt was lost through vomiting The treatment did, nevertheless, maintain kidney excretion for five days The rate of nitrogenous accumulation in the blood was markedly slowed, and the animal lived for eight days This favorable action on an overwhelming dose of the poison may be taken to indicate therapeutic value in the treatment It seems possible that with a less massive dose of mercury, life might be saved by repeated intravenous administration of hypertonic salt solution As we have previously stated, animals show marked variation in their reaction to small doses of mercuric chloride, and for this reason we do not have conclusive proof of this therapeutic action

TABLE 10—*Results of Intravenous Injections of 2 Mg of Mercuric Chloride Into Dogs 14 and 15*

| Dog | Day | Intravenous Injections of 1% Sodium Chloride, Cc | Mg per 100 Cc of Blood | | |
|-----|-----|--|------------------------|------------------|------------------------------|
| | | | Sodium Chloride | Urea Nitrogen | Total Nonprotein Nitrogen |
| 14 | 0 | 500 | 519.7 | 30.1 | 58.8 |
| | 1 | 500 | | | |
| | 2 | 500 | 407.0 | 80.2 | 108.4 |
| | 4 | 500 | 453.7 | 150.6 | 222.2 |
| | 7 | At death | 463.6 | 230.4 | 324.3 |
| 15 | 0 | No treatment | 500.0 | 12.4 | 40.5 |
| | 2 | No treatment | 331.4 | 70.2 | 142.8 |
| | 4 | No treatment | 343.2 | 170.4 | 214.2 |
| | 6 | No treatment | 240.9 | 245.4 | 376.2 |

CLINICAL APPLICATIONS

The foregoing results seem to indicate that hypochloremia should be an important consideration in mercury poisoning However, it must be remembered that dogs are animals which secrete a high concentration of hydrochloric acid into the stomach Furthermore, they are inclined to evacuate the stomach by vomiting at the least provocation This tendency no doubt makes them much more susceptible to a severe degree of hypochloremia than the average human patient During the course of our experiments, we did, however, observe one patient in whom there were significant changes in the blood chlorides

A woman of 20 years had placed a $7\frac{1}{2}$ grain (0.49 Gm.) tablet of mercuric chloride in the vagina four days before admission to the hospital There was a total suppression of urine, slight generalized edema, tenesmus and diarrhea and occasional vomiting The blood contained 193 mg of urea and 416 mg of sodium chloride per hundred cubic centimeters She was given daily gastric lavage and colonic irrigations of 5 per cent sodium bicarbonate Other treatment need not be discussed at this time After three days in the hospital, the urea had increased to 338 mg, and the sodium chloride had fallen to 368 mg per hundred cubic

centimeters of blood Thereafter, she was given daily intravenous transfusions of normal salt sufficient to maintain the blood chloride level above 400 mg per hundred cubic centimeters Her general condition was improved by this measure, but urinary suppression remained absolute until the twelfth day Following decapsulation of the right kidney on this day, there was an excretion of 900 cc of urine Following decapsulation of the other kidney on the fourteenth day, there was a slight reduction of nitrogenous elements in the blood, and the daily output of urine remained above 500 cc Death on the twentieth day seemed to result chiefly from a severe pelvic infection due to the extensive necrosis and sloughing of the external genitalia

There are several points of interest in this case, but we are concerned chiefly with the changes in the blood chlorides Though the hypochloremia was not allowed to become marked in this patient, it is certain that the reduction was too great to be accounted for by vomiting We believe that the loss in this case was brought about by colonic irrigations and gastric lavages with alkaline solutions The significance of this is evident In any condition which calls for routine lavage of the stomach or the intestinal tract, the danger of reducing the blood chlorides should be borne in mind The danger can no doubt be mitigated by including physiologic sodium chloride as a component of such solutions

We believe that any marked reduction of the blood chlorides is to be explained by loss from the gastro-intestinal tract In the case which we have cited, one other factor may have been responsible for the constant tendency to hypochloremia This patient showed a mild but progressive generalized edema This constant transudation of serous fluid must carry sodium chloride from the blood, and if disturbed alimentation prevents the intake of salt, a reduction of blood chlorides must occur

We have seen this mechanism strikingly demonstrated in a woman suffering from cirrhosis of the liver The terminal exacerbation of her portal obstruction caused anasarca and a rapid accumulation of ascitic fluid (from 2 to 6 liters were removed daily by paracentesis) After several days, she showed symptoms of tetany The sodium chloride in the blood was found to be 340 mg per hundred cubic centimeters It is apparent that a rapid transudation of fluid from the blood may produce a significant reduction of the chlorides

In the human patient poisoned with mercury, the tendency to edematous accumulations in the tissues may be a factor in producing hypochloremia We feel, however, that the chief cause is loss of chlorides from the gastro-intestinal tract

GENERAL SUMMARY AND CONCLUSIONS

- 1 Dogs poisoned by intravenous injections of mercuric chloride suffer a marked reduction in the sodium chloride of the blood, due to loss of chlorides through vomiting

2 This hypochloremia, though associated with a relative acidosis, produces gastric tetany. The tetany, therefore, is not a symptom of alkalosis, but occurs in any condition of hypochloremia without direct relationship to the carbon dioxide combined in the plasma.

3 Restoration of the blood chloride level relieves and prevents tetany but does not otherwise modify the course of mercury poisoning. There is some evidence that 2 per cent salt solution administered intravenously may be of value by forcing excretion from the kidney.

4 In the human patient poisoned with mercury, the danger of a low level of blood chlorides should be borne in mind. Other clinical applications have been discussed.

THE INFLUENCE OF ALKALIS ON THE SECRETION AND COMPOSITION OF GASTRIC JUICE

III THE EFFECT OF SODIUM BICARBONATE ON THE GASTRIC RESPONSE TO HISTAMINE *

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Various writers have stated that the antacid effect of sodium bicarbonate depends not only on the direct neutralization of hydrochloric acid, but also on a reduction of the amount of acid secreted in the stomach. For massive doses of the salt, this depression of gastric secretion was confirmed in some previously published experiments of mine.¹ The minimum amount of bicarbonate which could be depended on to produce this effect, however, was found to be about 1 Gm per kilogram of body weight, whether given as a single dose after a meal, or as the total daily dose for dogs on prolonged feeding with alkali. With smaller doses of bicarbonate, within the limits of ordinary antacid medication, the secretory response to a meal was on the average slightly greater than that found in the control experiments.

If the human stomach is as little affected by alkalis as is that of the dog, depression of secretion is probably not a factor in any therapeutic action which sodium bicarbonate may have. If this is given to an adult, the minimum daily amount which might be expected to reduce secretion would be from 50 to 75 Gm. Keefer and Bloomfield² have recently found that doses of from 1 to 2 Gm do not have any apparent effect on secretion in man.

In the present investigation, I have again studied the effect of single doses of bicarbonate, using amounts considerably greater, in proportion to body weight, than those given by Keefer and Bloomfield to human subjects. Instead of food as a gastric stimulant, a standard dose of histamine (1 mg of the dihydrochloride) was injected subcutaneously. This procedure gives a response which is more constant quantitatively than that obtained from repeated feeding of a standard meal.³

* From the Department of Physiology and Pharmacology, Loyola University School of Medicine

1 Boyd, T E. The Influence of Alkalies on the Secretion and Composition of Gastric Juice. I. The Effect of Prolonged Administration of Sodium Bicarbonate and Calcium Carbonate, *Am J Physiol* **71** 455 (Jan.) 1925, II. The Effects of Single Doses of Sodium Bicarbonate and Calcium Carbonate, *ibid*, p 465

2 Keefer, Chester S., and Bloomfield, A L. A Quantitative Study of the Effect of Sodium Bicarbonate on Gastric Secretion, *Bull Johns Hopkins Hosp* **39** 379 (Dec.) 1926

3 Lim, R K S. On the Relation Between the Gastric Acid Response and the Basal Secretory Rate in the Stomach, *Am J Physiol* **69** 318 (July) 1924

Some work has also been done to determine whether or not the alkali affects secretion locally by contact with the gastric mucosa. In the experiments referred to in this paper,¹ the bicarbonate was in all instances fed by mouth, and the juice was collected from a separated pouch. Pavlov's work indicates that the secretion of the pouch parallels that of the main stomach, but this relation may not hold true under all conditions.

EXPERIMENTAL WORK

Administration of Bicarbonate by Mouth—Two Pavlov pouch dogs were used, the weights being respectively 10.2 and 11.4 Kg. During the experimental periods they were kept on a diet of milk and white bread. The alkali was given in 2.5 or 5 per cent solution of water, by a stomach tube. When this involved giving more than 200 cc of liquid, it was

TABLE 1—Cubic Centimeters of Gastric Juice Collected After the Administration of 1 mg of Histamine Dihydrochloride

| | Weight, Kg | Controls | 10 Gm Sodium Bicarbonate in 400 Cc Water | 10 Gm Sodium Bicarbonate in 200 Cc Water | 10 Gm Sodium Bicarbonate in 200 Cc with Water ad lib |
|--------|---------------|--|--|--|---|
| Dog 40 | 10.2 | 15.0 23.0 18.3 20.1 22.1 20.7 18.7 | 22.3 22.3 18.7 | 6.0 11.2 7.9 11.5 | 19.7 15.0 12.5 15.5 |
| Mean | | 19.7 | 21.1 | 9.2 | 15.7 |
| Dog 38 | 11.4 | 17.0 18.2 21.0 17.2 18.5 | 19.7 17.5 23.2 23.0 | 10.3 12.1 13.3 | 16.8 19.0 19.4 13.5 |
| Mean | | 18.4 | 20.9 | 11.9 | 17.2 |

divided into two or more portions, given one hour apart. The histamine was administered one hour after the last dose of alkali, and the gastric juice was collected for two hours following. The secretion in response to the same dose of histamine was measured in control experiments without bicarbonate. Experiments were preceded by a period of from twelve to sixteen hours during which the animals were kept without food or water, and none were carried out when the resting or continuous secretion exceeded 4 cc per hour. An interval of at least forty-eight hours was allowed between the injections of histamine.

It was found (table 1) that the giving of 10 Gm of sodium bicarbonate (approximately 1 Gm per kilogram of body weight) in 2.5 per cent solution did not produce any diminution in the amount of juice secreted after an injection of histamine. The acidity of the juice (not shown in the tables) likewise remained undiminished, always being near the maximum figure of 0.45 to 0.5 per cent free hydrochloric acid.

When the same dose of alkali was given in 5 per cent solution, without additional water, the secretion was reduced (column 3 in table 1) The procedure was then repeated, water being left in the cages for the animals to drink at will The secretion was increased until it almost equaled the average obtained in the control experiments (column 4, table 1)

Because of this difference in effect between the dilute and concentrated solutions, it seemed likely that the latter acted through some influence on the water supply to the gastric glands According to this hypothesis, a saline cathartic in concentrated solution might be expected to have a similar depressing effect on secretion Table 2 shows the result of administering histamine one hour after the giving of 15 Gm of magnesium sulphate in 100 cc of water

TABLE 2—*Cubic Centimeters of Gastric Juice Collected After the Administration of 1 mg of Histamine Dihydrochloride Experimental Conditions Described in Text*

| | Weight, Kg | 20 Gm Sodium Bicarbonate Water ad lib | 15 Gm Magnesium Sulphate 100 Cc Water | Irrigation of Pouch with Sodium Bicarbonate Solution |
|--------|---------------|---|---|--|
| Dog 40 | 10.2 | 5.2 2.0 12.7 11.0 | 10.1 8.7 11.8 | 26.2 17.0 11.7 26.5 20.3 19.8 27.0 24.7 |
| Mean | | 7.7 | 10.2 | 21.6 |

Large doses of sodium bicarbonate (2 or more grams per kilogram) depress secretion even when unlimited water is allowed (table 2, column 1) The giving of such amounts is often followed by vomiting, and experiments in which this occurred are omitted from the tables

The Question of a Direct Action of Sodium Bicarbonate by Contact with the Gastric Mucosa—One dog was trained to lie quietly on the table while the pouch was being irrigated with a solution of sodium bicarbonate The fluid was delivered at the inner extremity of the pouch through a small bent glass tube, which passed along the lumen of a larger rubber tube The latter was closed at its inner end, except for a small opening through which the glass tube projected The solution thus flowed out toward the fistula in contact with the mucosa Just within the fistula it reentered the large tube, through perforations, and drained out The inflowing solution was siphoned from a large container in which it was kept at from 37 to 39 C, the temperature never varying beyond those limits Concentrations of 2.5 and 5 per cent were used The irrigation was maintained for one hour, about 600 cc of solution flowing

through in that time. The alkali was finally washed out with 25 cc of water at 38 C, and the pouch allowed to drain for ten minutes with the dog on its feet. Histamine was then administered and the gastric juice collected for the usual period of two hours.

The last column in Table 2 shows the results. The average figure is slightly greater than that found in the controls, but the difference is perhaps not great enough to be of any significance. There is at any rate no evidence of diminished secretory activity in the pouch.

COMMENT

Most of the numerous experiments in this field have dealt with the influence of the alkalis on the gastric response to some standard meal. This response varies from day to day under the most constant conditions yet obtained. Failure to take these variations sufficiently into account is probably responsible for most of the conflicting statements regarding the effect of the alkalis. Histamine has not previously been used in the study of this problem, so far as I can learn. Bickel⁴ used pilocarpine to stimulate secretion in dogs. He reported that sodium bicarbonate would stop such secretion in progress, and prevent any response to a second administration of pilocarpine. Details as to dosage or number of experiments were not given, so it is not possible to compare his observations with those here presented. The results given in this paper with those of my earlier papers, indicate that as a means of reducing gastric secretion moderate doses of sodium bicarbonate are ineffective unless water is withheld. The amount, up to about 1 Gm per kilogram of body weight, seems to be of less importance than the concentration. Doses above this range may depress secretion or even stop completely the formation of acid. Such massive doses, however, may produce some rather unpleasant symptoms in human subjects.⁵

The control experiments may be criticized on the ground that no water was allowed for twelve hours before the histamine was administered, while 200 cc or more of water was given with each feeding of alkali. The effect of water as a gastric stimulant is well known. It augments the secretory response to food⁶ and would doubtless increase the average volume of juice secreted following histamine. A 25 per

4 Bickel, A. Experimentelle Untersuchungen über den Einfluss von Alkalien und Säuren auf die sekretorische Funktion der Magenschleimhaut, *Berl klin Wchnschr* **42** 869, 1905.

5 Hardt, L. L., and Rivers, A. B. Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, *Arch Int Med* **31** 171 (Feb 15) 1923. Kast, Ludwig, Myers, V. C., and Schmitz, H. W. Clinical Conditions of Alkalosis, *J A M A* **82** 1858 (June 7) 1924.

6 Ivy, A. C. Contributions to the Physiology of the Stomach. XLVIII. Studies in Water Drinking, *Am J Physiol* **46** 420 (July) 1918.

cent solution of bicarbonate has no such effect if given before histamine, and I have elsewhere reported¹ that a 2.5 per cent solution of sodium bicarbonate, given on the empty stomach, is a much less effective stimulant of gastric secretion than is an equal volume of water. Sodium bicarbonate in such concentrations may then be said to prevent the water in which it is dissolved from acting as a stimulant. Only in this sense can it be said to have a depressing effect.

SUMMARY

1 Sodium bicarbonate given in 2.5 per cent concentration in amounts up to 1 Gm. per kilogram of body weight does not affect the gastric response to a subsequent stimulation by histamine.

2 The same amount of sodium bicarbonate given in 5 per cent concentration reduces the secretion caused by histamine. It is believed that this effect is due mainly to dehydration.

3 Massive doses (2 or more grams per kilogram of body weight) reduce the response to histamine regardless of water allowance.

4 The application of solutions of sodium bicarbonate (2.5 and 5 per cent) to the gastric mucosa for one hour periods does not affect the response of the mucosa so treated to subsequent stimulation by histamine.⁷

7 The histamine dihydrochloride used was supplied through the courtesy of Dr. M. T. Hanke, of the Otho S. A. Sprague Memorial Institute of the University of Chicago.

I wish also to thank Mr. Byford F. Heskett for assistance in some of the experimental work.

THE AUSCULTATORY GAP IN SPHYGMOMANOMETRY

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The clinical importance and the finding of only a rare reference in the English language to the auscultatory gap in sphygmomanometry indicate the need of a detailed presentation of the subject. For this purpose we have studied thirty cases.

The auscultatory gap, "le trou auscultatoire" of the French, is that interval of absolute or relative silence occasionally found on listening over an artery during deflation of the blood pressure cuff, it usually begins at a variable point below the systolic pressure and continues for from 10 to 50 mm of mercury.

LITERATURE

In 1917, Cook and Taussig¹ reported a period of complete silence during the second phase of determination of blood pressure by the auscultatory method. They estimated that this phenomenon occurred in 5 per cent of hypertensive cases. In 1918, Tixier^{1a} noted a short zone of silence below the systolic pressure.

In 1919, Gallavardin and Tixier² recorded one case of auscultatory gap and in the following year Poulain³ added reports of six others. All of these cases, however, were associated with aortic stenosis.

In 1920, Etienne and Richard,⁴ and Lian⁵ discussed the occurrence of the auscultatory gap in conditions other than aortic stenosis, chiefly in cases of hypertension.

1 Cook, J E, and Taussig, A E. Auscultatory Blood Pressure Determination, A Source of Possible Error, *J A M A* **68** 1088 (April 14) 1917.

1a Tixier, L. La méthode auscultatoire en sphygmomanométrie, *Paris méd* **27** 449, 1918.

2 Gallavardin, L, and Tixier, L. Dissociation sphygmomanométrique oscillatoire et vibro-auscultatoire dans un cas de rétrécissement aortique serré et insuffisance aortique avec pulsus tardus et anacrotisme, *Arch d mal du coeur* **12** 447, 1919.

3 Poulain, P. Deux signes sphygmomanométriques du rétrécissement aortique, trou auscultatoire et labilité tensionnelle systolique, Thèse Lyon, 1920.

4 Étienne, G, and Richard, G. A propos de deux cas de dissociation sphygmomanométrique, *Rev méd de l'est* **48** 460, 1920.

5 Lian, C. Étude critique des méthodes sphygmomanométriques et présentation d'un phono-sphygmomètre, *Bull et mém Soc méd d hôp de Paris* **44** 1643, 1920.

In 1920, Gallavardin and Tixier⁶ and in 1921, Gallavardin and Barbier⁷ reported that the auscultatory hole was found occasionally in patients exhibiting aneurysm or compression of the subclavian or brachial artery, and that it was not infrequently observed in marked hypertension

In 1921, Molle⁸ described a silent area in or near the center of the pulse pressure, and reported five cases in which the auscultatory gap was unilateral

In 1926, two English authors, Dally⁹ and Heatherly,¹⁰ mentioned the auscultatory gap in their books on cardiovascular disease but did not describe it in detail

It will be recalled that in 1905 Korotkoff¹¹ suggested the value of auscultation in the determination of blood pressure. He called attention to the fact that while the pressure in the cuff was gradually reduced from above the systolic value, a succession of sounds could be heard over the artery distal to the cuff. He originally distinguished four phases of sound, subsequently, one phase was divided, so that five phases are now differentiated, as shown diagrammatically in figure 1. The initial phase, characterized by sharp sounds, is apparently due to the sudden distention of the collapsed artery caused by the return of the pulse wave. The beginning of this phase indicates the systolic pressure. In the second phase, a murmur is superimposed on the sound, probably due to whorles or eddies in the blood current as it traverses the arterial constriction and drops to a lower pressure on entering the uncompressed portion of the artery below the cuff. In the third phase, the murmur disappears and the sounds become louder and more intense, due probably to sudden vibrations of the vascular wall produced by an increased volume of blood flow. After reaching a maximum, these sounds abruptly lose their special character. The beginning of the fourth phase is the auscultatory index of the diastolic pressure. The sounds during this phase are muffled, dulled and inconstant, and sometimes are barely audible. At this time the external pressure is probably insufficient to cause distortion of the artery, the latter remaining filled

6 Gallavardin, L., and Tixier, L. La methode auscultatoire moyen d'etude du mode de repletion arterielle, trous auscultatoires, *Paris med* **37** 25, 1920

7 Gallavardin, L., and Barbier, J. Le trou auscultatoire et ses conditions de production, *Lyon med* **130** 605, 1921. Barbier, J. Pathogenie de la zone des souffles de la courbe auscultatoire, *Arch d mal du coeur* **14** 541, 1921

8 Molle, M. Le trou auscultatoire, *Bull med Paris* **35** 925, 1921

9 Dally, H. High Blood Pressure, Its Valuation and Control, New York, William Wood & Co., 1926

10 Heatherly, F. Modern Methods in the Diagnosis and Treatment of Heart Disease, New York, William Wood & Co., 1926

11 Korotkoff, N. S. Tr Imp Mil Med Acad St Petersburg, **11** 542, 1905

during diastole. The fifth phase of silence follows. Although this series of sounds is usually heard when there is good functional equilibrium between the heart and arteries, there are frequently individual variations.

TYPES OF AUSCULTATORY GAP

There are three types of gap in auscultatory sphygmomanometry. The first, the complete gap, appears to be the most common, and presents a zone of absolute silence in the auscultatory curve between two sonorous points. The second, the incomplete gap, is not infrequently observed, and is represented by a zone of marked diminution in the intensity of the normal sounds or murmurs. In the third, the variable type of gap,

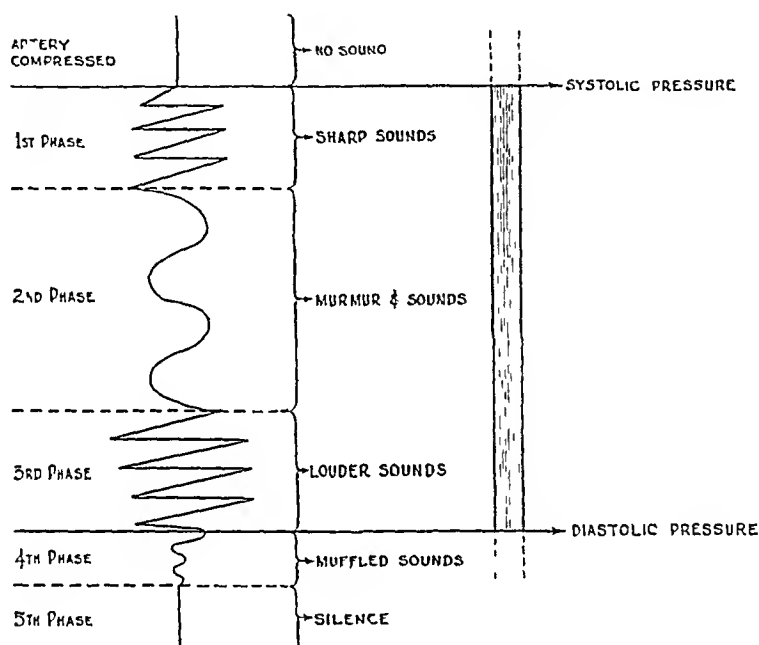


Fig 1—Diagrammatic representation of the five sound phases in auscultatory sphygmomanometry

there is no fixed hiatus in the auscultatory curve, but an inconstant diminution of the sounds may occur, dependent on changing conditions of the pulse, ventricular contraction or tonicity of the arteries. The differentiation between the three types is not always definite.

The silent zone is most frequently observed in the second, or murmur, phase, however, it may be found nearer the upper or the lower limit of the pulse pressure. Occasionally, when the auscultatory hole occurs near the maximal arterial pressure, there may be a so-called dissociation between the auscultatory and palpatory method in sphygmomanometry indicating, as shown in one of our cases, a systolic pressure of 200 mm by the palpatory method and a maximal pressure of 180 mm by the auscultatory method. The gap rarely occurs near the diastolic end of the auscultatory curve.

PRESENT SERIES OF CASES

In our series of thirty cases, as shown in figure 2, the average systolic blood pressure was 205 mm, with a range of from 140 to 280. The average diastolic pressure was 97 mm, the variation being from 20 to 150. The average pulse pressure was 108 mm, with a range of from 65 to 160. The average upper limit of the auscultatory gap was 177 mm, the variation being from 110 to 200. The average lower limit of the gap was 150 mm, with a range of from 90 to 190. The

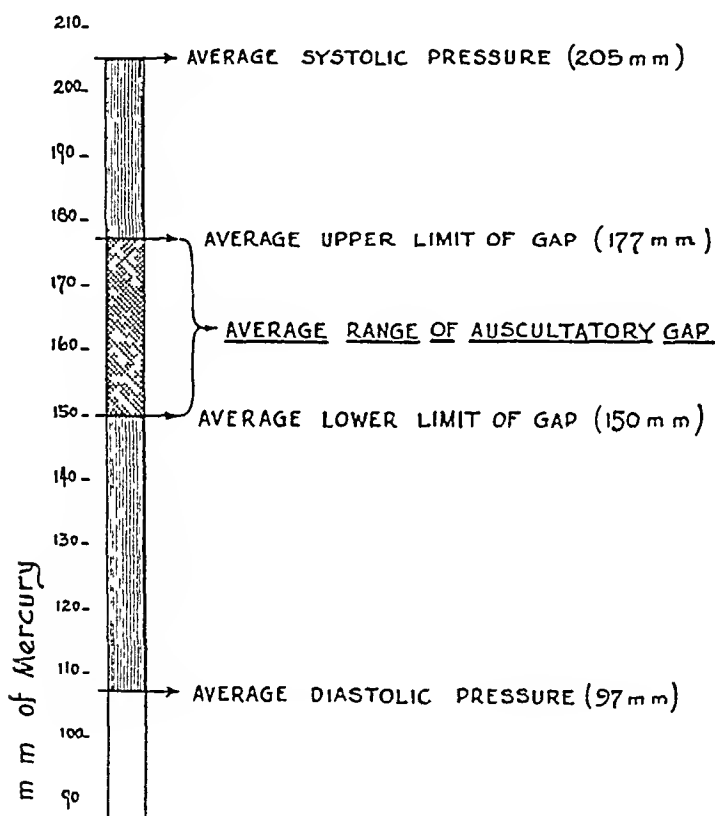


Fig 2—Average systolic and diastolic pressure in a series of thirty cases, showing the average range and position of the auscultatory gap

average extent of the auscultatory hole was 27 mm, the smallest gap was 10 and the largest 50.

In 18 (60 per cent) of our thirty cases, the gap occurred in the upper third of the pulse pressure, in eleven cases (37 per cent), the silent zone was found in the middle third, and in one case (3 per cent), in the lower third of the pulse pressure.

In our series the auscultatory gap was complete in twenty-six cases (87 per cent) and incomplete in four cases (13 per cent). The latter type occurred in patients who had evident hypertension in each instance. There was occasional variability between the two arms, the gap being

more easily demonstrated on one side. Observations on the same patient during repeated visits showed inconstant variations in the presence and position of the gap in several instances.

The auscultatory gap is of considerable clinical importance because of the error that may be occasioned by disregarding the possibility of its occurrence. The most frequent mistake is in the determination of the systolic pressure. If while taking the blood pressure of a person in whom an auscultatory gap is present the pressure is not carried above the gap, the systolic tension may be observed to be far lower than its actual value, since the unwary observer may falsely interpret the lower limit of the gap as the systolic pressure. On the other hand, if the cuff is inflated to a pressure high enough to obtain the correct systolic tension, the beginning of the upper limit of the gap may be mistaken for the diastolic pressure.

Classification of Diagnoses in Thirty Cases Exhibiting Auscultatory Gap

| Diagnosis | No. Cases | Per Cent |
|--|-----------|----------|
| Hypertensive and arteriosclerotic heart disease (two cases of complete heart block are included) | 13 | 43 |
| Essential hypertension with cardiac enlargement without evident arteriosclerosis | 7 | 23 |
| Rheumatic and hypertensive heart disease (two cases of aortic stenosis are included) | 5 | 17 |
| Essential hypertension without evident cardiac enlargement or arteriosclerosis | 2 | 7 |
| Rheumatic heart disease, with aortic stenosis | 2 | 7 |
| Syphilitic and hypertensive heart disease | 1 | 3 |
| Hypertension (total cases) | 28 (93%) | |
| Aortic stenosis (rheumatic, total cases) | 4 (13%) | |

The auscultatory hole is not demonstrable in the oscillometric method or by palpation of the radial pulse, and therefore these are valuable checks to prevent error occasioned by the occurrence of the gap.

In our group of thirty cases, as shown in the table, a diagnosis of hypertensive and arteriosclerotic heart disease was made in thirteen (43 per cent). Two cases of complete heart block are included in this group. In one of these, myxedema and syphilis were also present (This is the only case in which autopsy was performed, and in this instance the clinical diagnosis was confirmed). Essential hypertension with cardiac enlargement but without evident arteriosclerosis occurred in seven cases (23 per cent). Rheumatic and hypertensive heart disease was present in five cases (17 per cent), and of these, two showed aortic stenosis. Essential hypertension without evident cardiac enlargement or arteriosclerosis was diagnosed in two cases (7 per cent). Rheumatic heart disease with definite aortic stenosis was also found in two cases (7 per cent). Syphilitic and hypertensive

heart disease was present in one case (3 per cent). Thus, hypertension was evident in a total of twenty-eight cases (93 per cent), three of which were associated with chronic nephritis. Aortic stenosis on a rheumatic basis occurred in a total of four cases (13 per cent), three of which showed evidence of aortic regurgitation. Thus hypertension, aortic stenosis, or both, occurred in every case.

In our series thirteen (43 per cent) of the patients were men and seventeen (57 per cent) women. The average age was 56, the youngest patient being 31 and the oldest 79. The average pulse rate was 78, with a range from 36 to 100.

Variable symptoms were noted, the most important ones were dyspnea on exertion in sixteen cases (63 per cent), palpitation following effort, eleven cases (37 per cent), and angina pectoris and congestive failure six cases each (20 per cent). The arterial walls were slightly thickened in five cases (17 per cent), and moderately thickened in two cases (7 per cent). Arcus senilis was noted in three patients (10 per cent).

COMMENT

Cook and Taussig¹, Gallavardin and Barbier⁷, Gallavardin and Tixier¹² and Molle⁸ have advanced theories as to the mechanism involved in the production of the auscultatory gap. Five factors are worthy of note: first, a point of constriction in the artery through which the blood passes; second, a decrease in the pressure gradient below the point of constriction as compared with the pressure above; third, the type of pulse wave; fourth, failure of resonance of the arterial wall; and fifth, the peripheral resistance and vascular tone of the artery.

In 1916, Erlanger¹³ arranged a compression chamber and a stethoscope on the isolated femoral artery of the dog and demonstrated that the sounds in the first and second phases become faint and often disappear if the artery below the stethoscope is temporarily occluded.

The explanation of the auscultatory hole in hypertensive cases may be related to a type of pulse wave showing slight anacrotism or plateau form, as indicated in figure 3 which represents a brachial pulse tracing of a patient who had essential hypertension, coronary sclerosis and complete heart block but without a demonstrable aortic lesion. Failure of resonance of the arterial wall may be an additional factor in the hypertensive group. Furthermore, if there is increased peripheral resistance in the hypertensive cases, the blood pressure during the second phase when the flow into the artery distal to the cuff is ordinarily rapid, may

12 Gallavardin and Tixier (footnotes 2 and 6)

13 Erlanger, J. Studies in Blood Pressure Estimations by Indirect Methods. II. The Mechanism of the Compression Sounds of Korotkoff, *Am J Physiol* 40:82, 1916.

mount, owing to the high peripheral resistance, to a height sufficient to cause the sounds to disappear for a definite interval and to become audible again when the louder sounds of the third phase develop

The gap that occurs in aortic stenosis is probably due to reduced velocity of the pulse wave through the arteries associated with slowly rising or plateau pulses, some of which show anacrotism. Figure 4, a brachial pulse tracing of a patient with rheumatic heart disease, illustrates this point. The valvular lesions in this case were aortic and mitral stenosis and regurgitation. The tracing was made while the

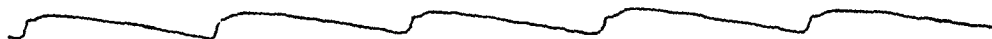


Fig 3—Brachial tracing of a patient who had essential hypertension, coronary sclerosis, and complete heart block, but without a demonstrable aortic lesion. The blood pressure was 180, systolic, 90, diastolic. The complete auscultatory gap was from 160 to 130 mm of mercury. Time interval = 0.2 second, every fifth mark being omitted.

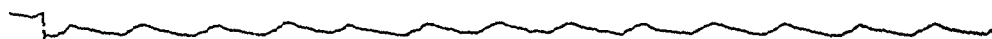


Fig 4—Brachial tracing of patient who had aortic and mitral stenosis and regurgitation (rheumatic heart disease) taken while the brachial artery was being decompressed and during auscultatory gap. The blood pressure was 150, systolic, 20, diastolic. The complete gap was from 120 to 90 mm of mercury. Time interval = 0.2 second, every fifth mark being omitted.

brachial artery was being decompressed and during the auscultatory gap, when the pressure in the blood pressure cuff was 110 mm of mercury. In the anacrotic pulse there is a rise of arterial pressure at the beginning of ventricular contraction, then a short interval of "dead point," during which the arterial pulse loses its vigor, and subsequently a second rise in arterial pressure until the maximal systolic tension is reached. Reduced velocity of the pulse wave accompanied by a slowly rising pulse may also furnish an explanation for the auscultatory gap when it is dependent on an aneurysm or compression of the subclavian or brachial artery.

SUMMARY

The clinical importance of the auscultatory gap in sphygmomanometry is emphasized because of the error that may be occasioned if the possibility of its occurrence is disregarded

A review of the literature is presented

Three types of auscultatory gap are considered (1) the complete gap, (2) the incomplete gap and (3) the variable type of gap

Thirty cases are reported and analyzed Hypertension was evident in twenty-eight patients (93 per cent) and aortic stenosis in four (13 per cent) Every case showed either hypertension, aortic stenosis, or both (2 cases)

Factors referable to the mechanism of the auscultatory hole are discussed

No definite prognostic significance is attached to the auscultatory gap, the outlook depending on the underlying pathologic condition in each case

THE EFFECT OF TOXEMIA ON TOLERANCE FOR DEXTROSE *

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AND

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The fact that toxemias, from whatever origin, cause a disturbance in the tolerance for dextrose of laboratory animals or human beings has been definitely established. This has been noted clinically and experimentally. Clinically, it is illustrated by the much feared infections of diabetic patients. The effect is that of producing a delay in the removal of dextrose from the blood stream or, in other words, a decreased tolerance. The exact explanation of this phenomenon is lacking. Lawrence and Buckley,¹ judging from a series of experiments on rabbits intoxicated with diphtheria toxin, are of the opinion that it is due to a glycogenolysis produced by a stimulation of the "thyroid adrenal apparatus." Tisdall and his co-workers,² experimenting with puppies intoxicated with diphtheria toxin and histamine, do not come to any definite conclusion regarding the explanation of this phenomenon. They feel that intoxication may produce its effect on the tolerance for sugar either by an increase in the glycogenolytic function of the body or by an impairment of the ability of the organism to store carbohydrates.

It occurred to us that a series of tests of the tolerance for dextrose of toxic animals with varying degrees of toxemia might give some information as to what extent their tolerance is disturbed and what the nature of the disturbance might be.

Rabbits were used for the experiments. A single injection of diphtheria toxin³ was given subcutaneously. A suitable dosage was determined to produce a toxemia that would cause the rabbit's death within from five to seven days. This dosage was found to be from 0.01 cc. to 0.0075 cc. of the toxin employed in the tests. All of the animals including the controls were starved during the experiments, in order to eliminate the effects of diet and to keep uniform the effect of the starva-

*From the Departments of Internal Medicine and Physiology, Baylor University College of Medicine

1 Lawrence, R. D., and Buckley, O. B. Brit J Exper Path **8** 1 (Feb) 1927

2 Tisdall, Frederick F., Drake, T. G. H., and Brown, Alan. Production of Lowered Carbohydrate Tolerance in Dogs, Am J Dis Child **32** 854 (Dec) 1926

3 I am indebted to the Eli Lilly Company, who supplied the diphtheria toxin

tion (One of us ⁴ has previously reported the effect of diets on tolerance for dextrose) On the day preceding the administration of dextrose, all food was removed from the animals' cages Water was allowed On the following day, a test of the tolerance for dextrose was made on each animal Five grams of dextrose in 25 cc of water was

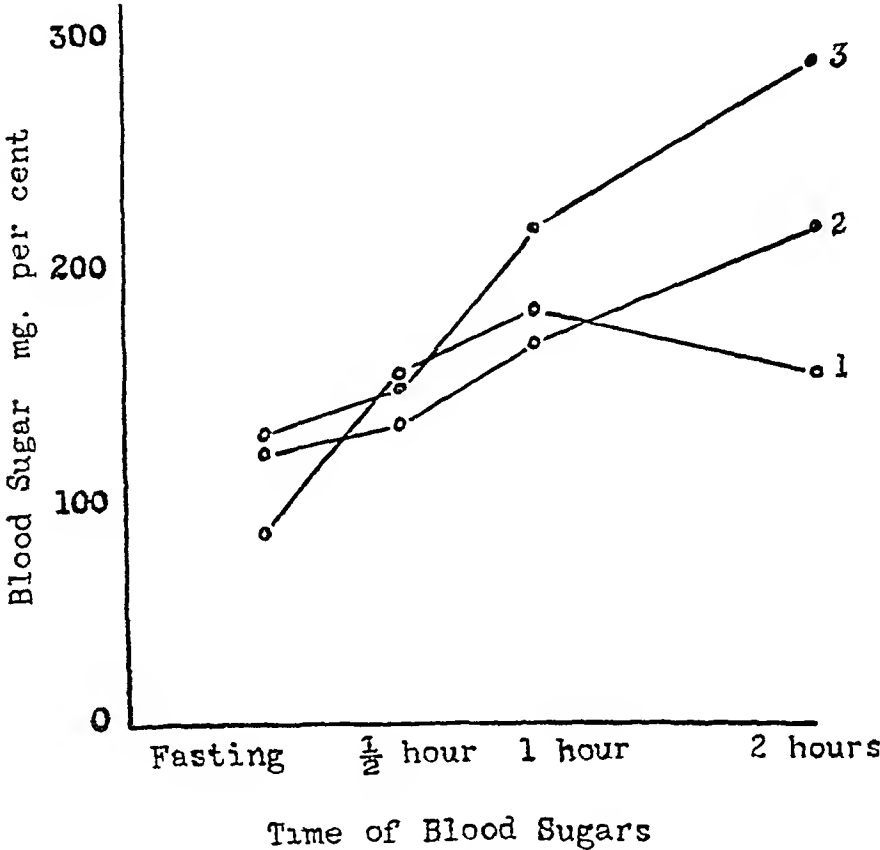


Chart 1—Daily curves showing the tolerance for dextrose of rabbit 2 following subcutaneous injection of 0.012 cc of diphtheria toxin (minimum lethal dose equals 0.03 cc) The numbers at the end of each curve indicate the day of toxemia

TABLE 1—Results of Daily Tests of Tolerance for Dextrose on Rabbit 2 Following Subcutaneous Injection of 0.012 cc of Diphtheria Toxin (Minimum Lethal Dose Equals 0.03 cc)

| Hours of Starvation | Hours of Toxemia | Temperature (F) Rectal | Blood Sugar, Mg per 100 Cc | | | |
|---------------------|------------------|------------------------|----------------------------|----------------|------------|-------------|
| | | | Fasting | After Dextrose | | |
| | | | | 30 Minutes | 60 Minutes | 120 Minutes |
| 48 | 24 | 106.4 | 89 | 152 | 179 | 152 |
| 72 | 48 | 102.6 | 111 | 129 | 167 | 211 |
| 96 | 72 | 103.5 | 120 | 149 | 211 | 286 |

4 Sweeney, J Shirley Dietary Factors that Influence the Dextrose Tolerance Test Arch Int Med to be published

then given by stomach tube to each rabbit. Samples of blood were drawn from the marginal veins of the ear for determinations of the sugar content before the administration of the dextrose and thirty, sixty and one hundred and twenty minutes following. In this manner, tests of the tolerance for dextrose were run every twenty-four hours until the death of the animals, in order to observe the effect of an increasing

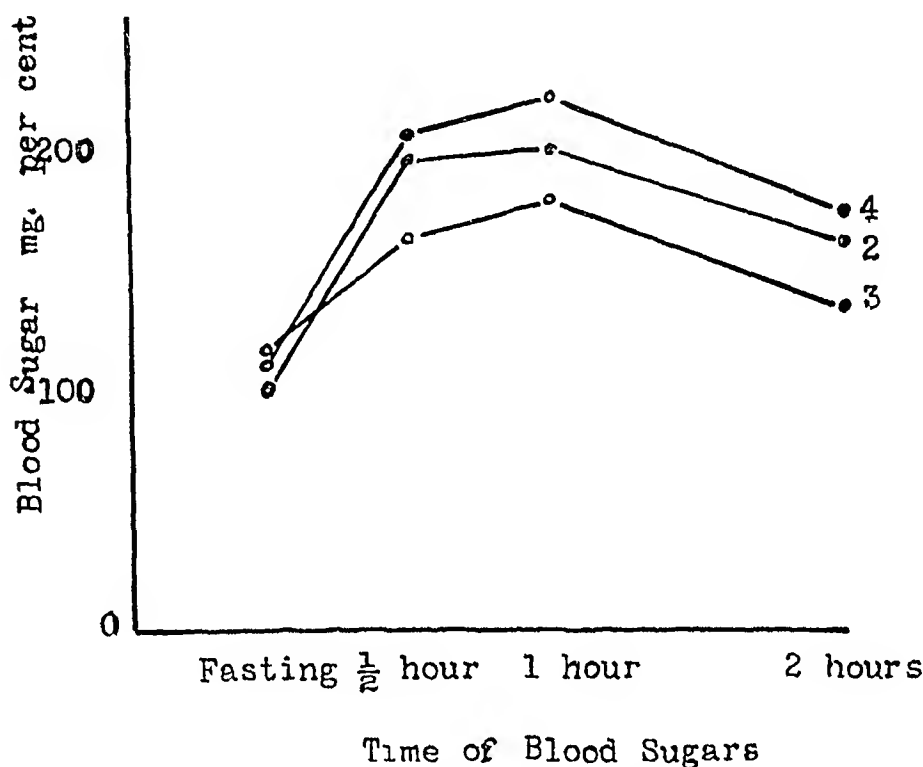


Chart 2—Daily curves showing the tolerance for dextrose of rabbit 4. Toxin was not given. The numbers at the end of each curve indicate the day of starvation.

toxemia.⁵ Control or nontoxic rabbits were treated in the same way. Rectal temperatures were taken daily at the end of each test.

TABLE 2—Results of Daily Tests of Tolerance for Dextrose on Rabbit 4, Used as Control for Rabbit 2, Table 1. Did Not Receive Toxin.

| Hours of Starvation | Temperature (F) Rectal | Blood Sugar, Mg per 100 Cc | | | |
|---------------------|------------------------------|----------------------------|----------------|------------|-------------|
| | | Fasting | After Dextrose | | |
| | | | 30 Minutes | 60 Minutes | 120 Minutes |
| 48 | 104 | 100 | 196 | 200 | 157 |
| 72 | 102.8 | 111 | 160 | 182 | 136 |
| 96* | 103.3 | 107 | 204 | 217 | 174 |

* Rabbit was fed following this test and was apparently normal the next day.

⁵ There is some effect of the dextrose on the tests of the tolerance for dextrose performed day after day. This was noted in some control animals not included in this series. This phenomenon is being studied at present.

The results of these tests of tolerance for dextrose are listed in tables 1, 2, 3, 4 and 5 and presented graphically in charts 1, 2, 3, 4 and 5. It will be noted that only three toxic rabbits were used. The effect of the toxemia was so marked and so uniform that additional observations were considered unnecessary.

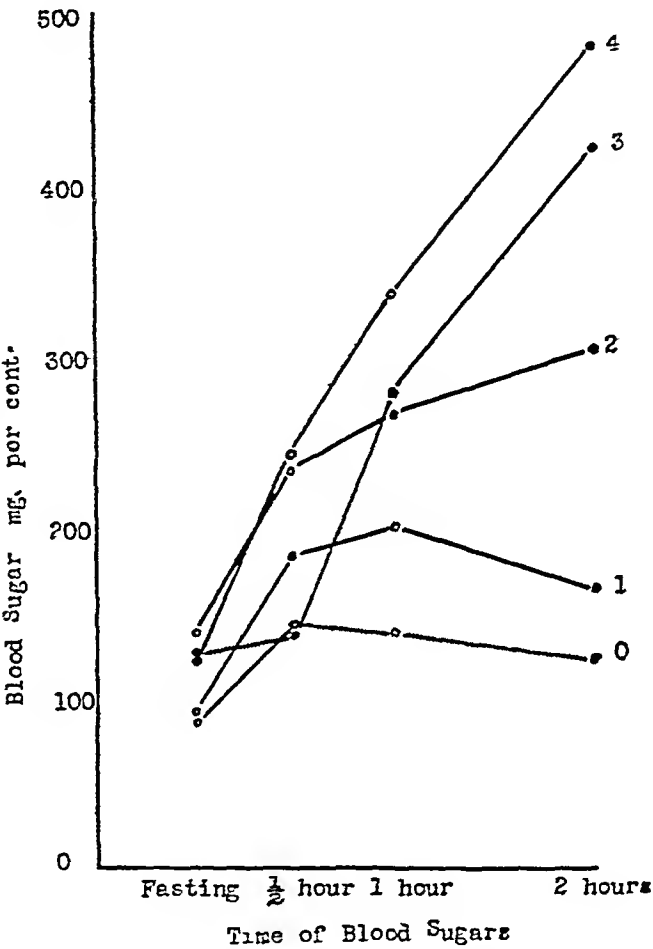
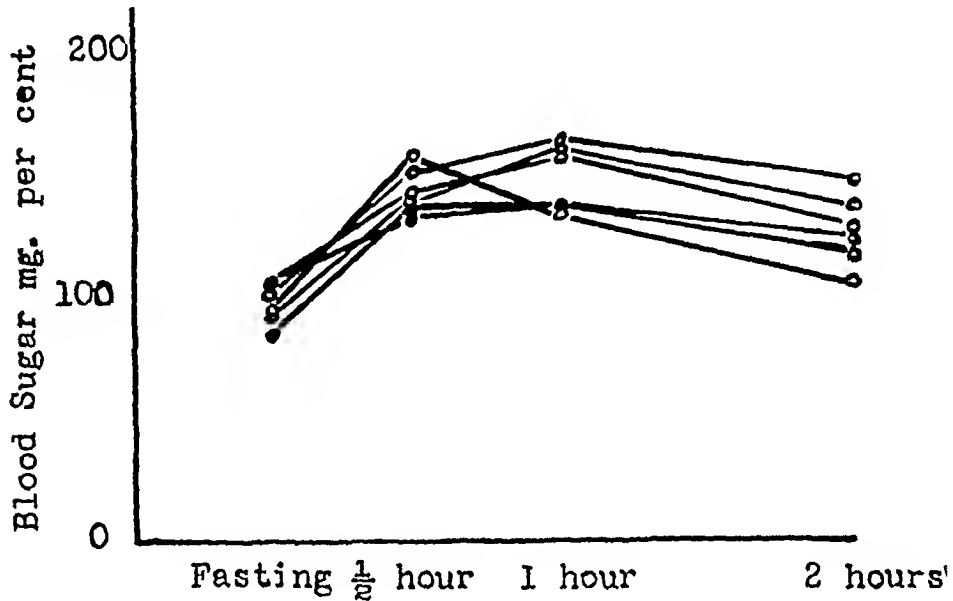


Chart 3—Daily curves showing the tolerance for dextrose of rabbit 8 following subcutaneous injection of 0.01 cc of diphtheria toxin (minimum lethal dose equals 0.03 cc). The numbers at the end of each curve indicate the day of toxemia.

TABLE 3—Results of Daily Tests for Tolerance for Dextrose on Rabbit 8 Following Subcutaneous Injection of 0.01 cc of Diphtheria Toxin (Minimum Lethal Dose Equals 0.03 cc)

| Hours of Starvation | Hours of Toxemia | Temperature (F) Rectal | Blood Sugar, Mg per 100 Cc | | | |
|---------------------|------------------|------------------------|----------------------------|----------------|------------|-------------|
| | | | Fasting | After Dextrose | | |
| | | | | 30 Minutes | 60 Minutes | 120 Minutes |
| 24 | | | 89 | 148 | 143 | 123 |
| 48 | 24 | 103.1 | 93 | 162 | 200 | 160 |
| 72 | 48 | 101.5 | 140 | 217 | 263 | 303 |
| 96 | 72 | 102.1 | 129 | 143 | 278 | 417 |
| 120 | 96 | 101 | 125 | 241 | 333 | 479 |

The most striking phenomenon to be noted is the positive association between the degree of toxemia (if it may be assumed that there was a daily increasing toxemia in the rabbits) and the impairment of the tolerance for dextrose. In other words, as the rabbits' toxemia became greater, their ability to remove the ingested dextrose from the blood stream became less. In no instance was there a suggestion of improved tolerance during the course of the toxemia. This would suggest that



Time of Blood Sugars

Chart 4—Daily curves showing the tolerance for dextrose of rabbit 5. Toxin was not given. The figures are given in table 4.

TABLE 4—Results of Daily Tests for Tolerance for Dextrose on Rabbit 5, Used as Control for Rabbits 8 and 7, Tables 3 and 5. Did not Receive Toxin

| Hours of Starvation | Temperature (F) Rectal | Blood Sugar, Mg per 100 Cc | | | |
|---------------------|------------------------------|----------------------------|----------------|------------|-------------|
| | | Fasting | After Dextrose | | |
| | | | 30 Minutes | 60 Minutes | 120 Minutes |
| 24 | | 103 | 133 | 138 | 125 |
| 48 | 103 | 92 | 156 | 133 | 105 |
| 72 | 103.1 | 82 | 135 | 138 | 114 |
| 96 | 103 | 100 | 150 | 167 | 148 |
| 120 | 103 | 103 | 143 | 154 | 123 |
| 144 | 103.8 | 95 | 141 | 160 | 132 |

there might be a quantitative relationship between toxemia and the tolerance for dextrose. Tisdall and his co-workers² did not make daily tolerance tests on their toxic animals. The degree of postprandial hyperglycemia of their animals from twenty-four to seventy-two hours following the injection of diphtheria toxin is in accord with the results presented in this study. There is apparently no uniform relationship

between temperature and tolerance for dextrose. If any such relationship exists, it appears to be that the tolerance is less when the temperature is at a lower level. It will be noted from the tables that this was true in a number of instances. Lawrence¹ noted this apparent relationship of temperature and the level of blood sugar in his studies.

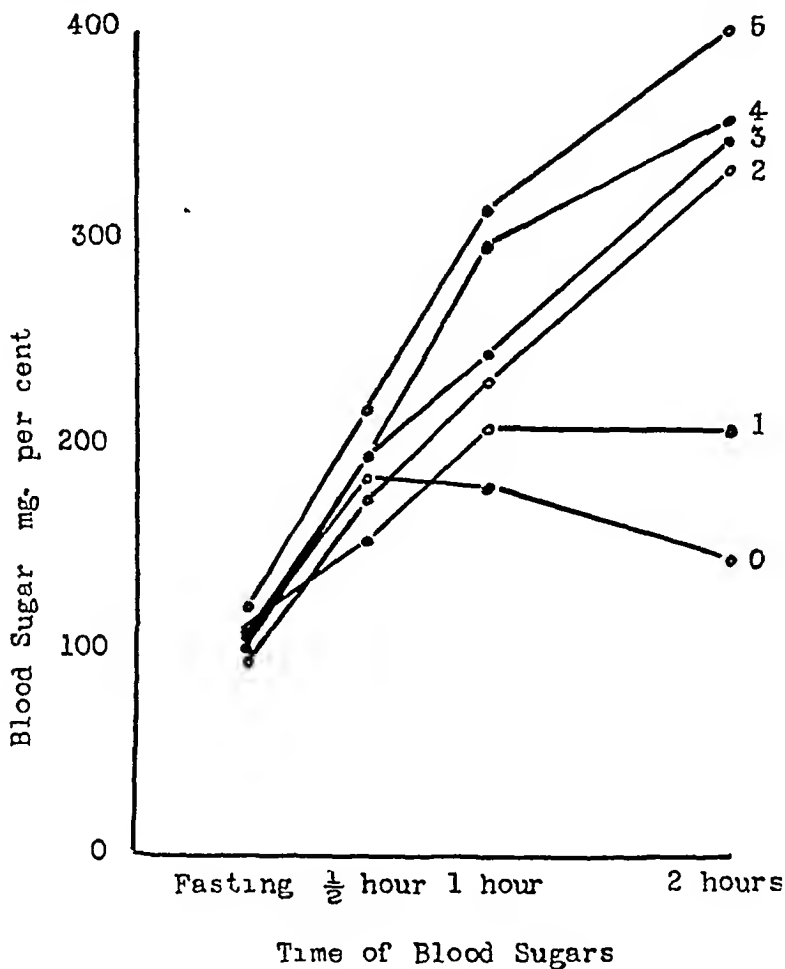


Chart 5—Daily curves showing the tolerance for dextrose of rabbit 7 following subcutaneous injection of 0.0075 cc of diphtheria toxin (minimum lethal dose equals 0.03 cc). The numbers at the end of each curve indicate the day of toxemia.

TABLE 5—Results of Daily Tests of Tolerance for Dextrose on Rabbit 7, Following Subcutaneous Injection of 0.0075 cc of Diphtheria Toxin (Minimum Lethal Dose Equals 0.03 cc)

| Hours of Starvation | Hours of Toxemia | Temperature (F) Rectal | Blood Sugar, Mg per 100 Cc | | | |
|---------------------|------------------|------------------------|----------------------------|----------------|------------|-------------|
| | | | Fasting | After Dextrose | | |
| | | | | 30 Minutes | 60 Minutes | 120 Minutes |
| 24 | | | 105 | 182 | 179 | 145 |
| 48 | 24 | 104.6 | 107 | 152 | 206 | 206 |
| 72 | 48 | 101.8 | 95 | 174 | 230 | 333 |
| 96 | 72 | 101.2 | 100 | 190 | 244 | 345 |
| 120 | 96 | 102.7 | 109 | 190 | 296 | 357 |
| 144 | 120 | 102.6 | 120 | 215 | 313 | 400 |

There is another interesting observation that is noteworthy in these studies, and that is that marked toxemias have little, if any, effect on the absorption of the orally administered dextrose. In one instance an animal died within a few hours after the test of its tolerance for dextrose had been finished and his two hour postprandial level of blood sugar was 400 mg per hundred cubic centimeters of blood. We believe that it may be concluded from this evidence that toxemias do not seriously interfere with the gastro-intestinal absorption of dextrose. One other observation is that toxemias cause a higher level of the blood sugar after fasting. This effect has been noted by many observers.

This phenomenon of the animals' increasing inability to remove the dextrose from the blood stream is probably to be explained in one of four ways: (*a*) by an increase in the glycogenolytic function of the body, (*b*) by an impairment of the glycogenic function, (*c*) by a suppression of the oxidative function and (*d*) by either a disturbance in the action or in the production of insulin, either of which is inextricably associated with one or all of the foregoing possibilities. Until the action of insulin is definitely determined, it must of necessity be difficult to explain these phenomena. We believe⁴ that the action of insulin is principally that of glycogenesis. If this be true, the most probable explanation of a decreased tolerance in the presence of a toxemia is some disturbance in the production or action of insulin. Experiments are now being completed that we believe will add weight to this hypothesis.

SUMMARY AND CONCLUSIONS

Rabbits made toxic by diphtheria toxin are shown to have a marked decrease in tolerance for dextrose. The decrease in tolerance becomes more marked during the course of the toxemia. This suggests a quantitative relationship between toxemia and tolerance for dextrose. It is suggested that the explanation of this phenomenon lies in a disturbance of insulin action or insulin production.

The toxemia did not have a noticeable effect on gastro-intestinal absorption of the dextrose.

HYPERTENSIVE ENCEPHALOPATHY *

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AND

ARTHUR M FISHBERG, M D

NEW YORK

In the course of acute glomerulonephritis and less commonly in other varieties of chronic interstitial nephritis, there may occur acute episodes of cerebral phenomena, such as epileptiform convulsions, coma, headache, amaurosis, hemiplegia and aphasia. In the past, these episodes were generally included under the concept of uremia and were termed acute uremia. Since the beginning of the present century, convincing evidence that these cerebral episodes are not uremic in nature has gradually accumulated. This evidence will be summarized later in the paper. It has become clear that these cerebral symptoms are correlated with hypertension, being a manifestation of circulatory disturbances in the brain consequent on the hypertension. For this reason, we have termed the cerebral syndrome the hypertensive encephalopathy. The nature of the hypertensive encephalopathy is well illustrated in the following case. We have had the patient under continuous observation over a period of twenty months at the Mount Sinai and Montefiore Hospitals.

REPORT OF A CASE

History—S S, a college student, aged 19, entered Mount Sinai Hospital, Sept 7, 1925, in an aphasic state following a convulsion four hours before entrance.

He had pneumonia when 8 years old. His tonsils were removed when he was 12. From then to January, 1925, he was perfectly well.

In January, he became ill with bronchopneumonia, and was confined to his bed for six weeks. Following his recovery, he again became sick, this time with acute rheumatic fever. Painful, swollen joints, fever and cardiac involvement, as evidenced by a diastolic murmur, were present. At this time, the patient's systolic blood pressure was 120 mm, and the urine did not contain any albumin. He seemed to have completely recovered by May 20, the blood pressure was normal and the urine free from albumin. About Aug 1, 1925, he began to suffer from frontal headaches which prevented him from sleeping. At this time, his family physician found that he had arterial hypertension and that his urine contained albumin and blood. The headaches became progressively worse, and to them were added attacks of vomiting. On September 7, following a period of restlessness, he had a severe convulsion. Four hours after the convulsion he was brought to the hospital, aphasic but conscious.

On admission, the patient was drowsy and apathetic. He was able to respond to questions only by repeating words used by the questioner. The pupils were equal and regular, the action of the left being the livelier. The heart was

* From the medical divisions of Mount Sinai and Montefiore Hospitals.

* Read in abstract before the Association of American Physicians, Atlantic City, New Jersey, May 3, 1927.

somewhat enlarged to the left, the forceful apex beat being felt in the fifth interspace outside the midclavicular line. The first sound at the apex was booming and was followed by a short systolic murmur. The second sound, at the aortic area, was greatly accentuated and clanging. The radials felt thickened and hard. The blood pressure was 200 mm systolic and 110 mm diastolic. The right knee reflex was livelier than the left, no Babinski sign or other pathologic reflexes were present. The urine had a specific gravity of 1.022, and contained a faint trace of albumin and a few granular casts. Examination of the blood showed hemoglobin, 106 per cent, red blood cells, 6,600,000, white blood cells, 28,000, polymorphonuclears, 88 per cent, lymphocytes, 6 per cent, and monocytes, 4 per cent. The Wassermann reaction was negative, and the blood culture proved sterile. The blood chemistry was nonprotein nitrogen, 31.4, urea nitrogen, 14.0, uric acid, 4.2, creatinine, 1.2 mg per hundred cubic centimeters.

Beginning at 3 a. m. of the night following admission, the patient had several right-sided convulsions. During these convulsions, each of which was of one or two minutes' duration, the head was turned to the right, the eyes rolled upward and to the right, and there were clonic movements of the right side of the face, right arm, trunk, and right lower extremity. Following these, there were generalized bilateral convulsions which were stopped by the administration of a little chloroform. At this time neither plantar nor abdominal reflexes could be elicited. The knee and ankle reflexes were active and equal, without clonus. The left pupil was larger than the right and reacted sluggishly with hippus. A phlebotomy of 400 cc. was carried out and lumbar puncture performed. It revealed the cerebrospinal fluid to be under normal tension, clear, and containing no cells.

The next morning the patient was extremely anxious, restless and inattentive. The left palpebral fissure was narrower than the right. The left pupil was larger than the right. Both pupils reacted sluggishly to light. There was slight facial weakness on the right. The right biceps and triceps reflexes were more active than the left. The knee reflexes were present. A bilateral Babinski sign and a tendency to a right ankle clonus were present.

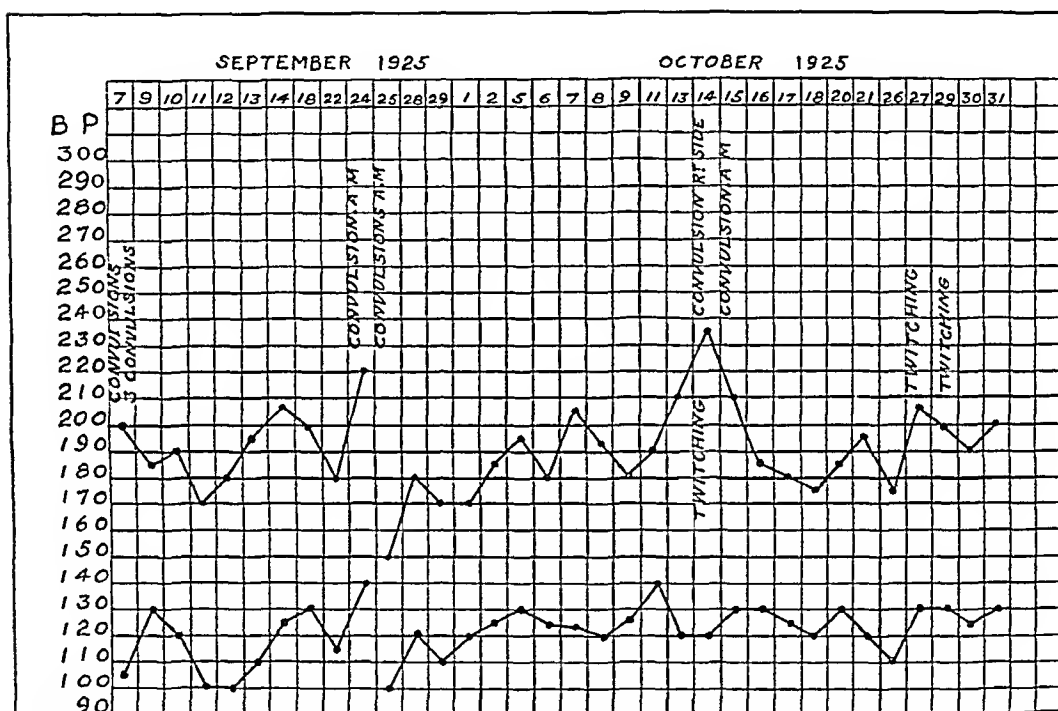
On ophthalmoscopic examination, the arterial blood columns appeared narrow, the vessel wall somewhat thickened. No other abnormalities were noted by the ophthalmologist.

The next day the patient was greatly improved and the Babinski reflexes had disappeared. The blood pressure was 190 systolic and 130 diastolic.

From Sept. 7, 1925, to April, 1927, we have had the patient under continuous observation, first in Mount Sinai and then in Montefiore Hospital and subsequently again at Mount Sinai Hospital. Our observations during this period were as follows:

Neurologic Phenomena.—From the time of his admission to December, 1926, a period of fifteen months, the patient had many convulsive seizures. Sometimes there were several in a day, once more than twenty, at other times a month would pass without one. From April 4, 1926, to Aug. 26, 1926, there were no convulsions. The convulsions were usually preceded by an aura, consisting of headache, a feeling of weakness and paresthesias in the right upper extremity in the form of a tingling in the fingers and "a feeling as though there is no blood in the right arm and hand, and they are paralyzed." From these prodromes, the patient often knew when an attack was imminent. On several occasions, the prodromes were not followed by actual convulsions. The convulsions usually started with tonic and then clonic spasms of the right upper extremity, which then spread to the right lower extremity and finally became generalized. How-

ever, among the later convulsions were some that started with paresthesias of the left upper extremity, which then began to twitch with subsequent involvement of the right side of the body. The convulsions were of varying duration, from a few quick twitches to severe attacks lasting five or more minutes. During the attacks, the patient would foam at the mouth and would appear extremely cyanotic. Consciousness was usually completely lost during the convulsions and for some time thereafter, though during a few mild seizures he remained conscious. On several occasions, the convulsions were quickly aborted by chloroform. The patient did not bite his tongue, but in one nocturnal attack it was necessary for the nurse to separate his clenched teeth with a gag. A few attacks consisted of only transitory pareses of the right upper extremity. Following the attacks, the patient was usually stuporous, but often recovered complete consciousness in a few minutes.



The relation of rises in blood pressure to convulsive seizures

Between convulsions and immediately after the attack, the pupils reacted slowly to light and sometimes hardly at all, occasionally, anisocoria was present. The tendon reflexes were hyperactive, and the Babinski reflex was present on both sides. The pupillary abnormalities and Babinski reflexes would disappear within a few hours, and between attacks there were no abnormal neurologic manifestations.

Blood Pressure—At first the blood pressure was about 200 mm systolic, and 110 mm diastolic, later it rose to an average of about 230 mm systolic and 130 mm diastolic, always being elevated. For several days before most, though not all, of the convulsive seizures, the blood pressure rose markedly, in some cases the rise being as much as 50 mm each of the systolic and diastolic pressures, as shown in the accompanying chart. After some of the attacks, the pressure fell decidedly, though only temporarily. Thus, in the week prior to the severe convulsive seizure of Sept 24, 1925, the pressure rose steadily from 170/140 to

220/140 a few hours before the attack, to fall to 150/100 several hours after the attack, the latter being the lowest pressure the patient ever showed

The pressure of the cerebrospinal fluid was determined on several occasions, the lumbar puncture being carried out either for the relief of convulsive seizures or headache, or to prevent an attack when prodromes were present. The pressure was either normal or only slightly elevated, the highest value being 30 cm of water.

Kidney function was carefully studied. At no time was there any evidence of serious impairment of renal function. At all times, the patient was able to concentrate the urine to a specific gravity of 1.022 or higher and to dilute normally. There was never any evidence of nitrogen retention, as is shown in the accompanying table.

On Oct. 23, 1925, the plasma chlorides were 540 mg per cent (as sodium chloride). On Dec. 6, 1926, the calcium content of the serum was 9.7 mg per cent and on April 5, 1927, 10 mg per cent.

The urine showed comparatively slight deviations from the normal. Most of the daily examinations revealed a trace of albumin, but this was never heavy, and on many examinations no albuminuria at all was present. Microscopic exami-

Blood Chemical Determinations

| Date | Nonprotein Nitrogen | Urea Nitrogen | Uric Acid | Creatinine | Cholesterol |
|----------|---------------------|---------------|-----------|------------|-------------|
| 9/ 8/25 | 31.4 | 14.0 | 4.2 | 1.2 | |
| 9/10/25 | 26.7 | 14.0 | 3.0 | 1.1 | |
| 11/23/25 | 38.5 | 15.4 | 3.5 | 1.0 | |
| 12/ 2/25 | 42.1 | 23.8 | 6.0 | 1.4 | |
| 1/11/26 | 35.0 | 11.2 | 3.5 | 1.1 | 142 |
| 2/ 2/26 | 28.0 | 12.6 | 6.5 | 1.5 | 200 |
| 3/ 5/26 | 26.7 | 11.2 | 4.0 | 1.0 | |
| 4/15/26 | 26.0 | 11.2 | 3.5 | 1.2 | |
| 5/19/26 | | 8.8 | | | 164 |
| 7/26/26 | | 9.7 | | | |
| 8/30/26 | | 8.4 | | | |
| 3/ 2/27 | 36.9 | 11.0 | 2.6 | | |

nation often showed a few hyaline and granular casts, but these were not always present. Red and white blood cells were never found in any considerable quantity, though the history states that the patient had had hematuria at the onset of his illness.

The Retina—When the patient first entered the hospital, ophthalmoscopic examination revealed only a narrowing of the arterial blood columns and some changes in the arterial walls as evidenced by thin white lines bordering some of the arterial blood columns. Then changes rapidly appeared, so that ten days later, the following symptoms were noted by the ophthalmologist, Dr. Goldstein: "O.D. the disk is hyperemic. Its margins are fairly distinct, the physiological pit large, and the veins about normal. The tortuous arteries are narrower than normal. To the nasal side of the disk are many irregularly round, grayish white patches about one half the size of the disk, they are situated in the deeper layers of the retina. The macula is very red, surrounded by a prominent light reflex on the temporal side. There are a few exudates on the temporal side. O.S. the disk is hyperemic with margins somewhat blurred. There is a large physiological cup. The veins are about normal in size, the arteries narrowed. The macula is normal. There are no exudates or hemorrhages."

The typical picture of "albuminuric retinitis" developed quickly, with a stellate figure around the right macula. There were numerous patches of exudate and hemorrhages on both sides. The most striking feature at all times was the

extreme narrowing of the arteries, rendering them difficult to recognize. Papilledema was present at times in slight degree, never becoming marked. The hemorrhages and exudates cleared up entirely during the next eighteen months except for the fine silvery white spots arranged radially around the right macula. The arteries were still narrow in April, 1927.

The patient was at Mount Sinai Hospital in April, 1927. He was ambulatory, though not strong. The vision was somewhat impaired by the albuminuric retinitis, but it was better than formerly and he read without any difficulty. The blood pressure had settled at a constant high level (about 240 systolic, 130 diastolic). No nitrogen retention was present. The last convulsions occurred during March, 1927, and no abnormalities were found on examination of the nervous system.

Summary—A youth, aged 19, became ill with pneumonia and acute rheumatic fever. Following recovery from these, it was found that the blood pressure was abnormally high and that the urine showed blood and albumin. In the twenty months since then, the blood pressure had remained high, but there had never been any nitrogen retention and in fact no evidence of impairment of renal function had appeared. During this period he had had many epileptiform convulsions from which he quickly recovered. In conjunction with these, he had had transient palsies and on one occasion transient aphasia. On several occasions, it was evident that the convulsive attacks marked the culmination of a period of rising blood pressure, which fell soon after the attack. The pressure of the cerebrospinal fluid was measured on several occasions between or soon after the convulsions, and was either normal or only moderately elevated.

The convulsive seizures in this case illustrate the most striking form of what we term the hypertensive encephalopathy, but generalized epileptiform convulsions are by no means the only way in which the hypertensive encephalopathy may manifest itself. Various other focal and general cerebral symptoms may occur, either in combination with or independent of the convulsions. The convulsions may be unilateral, simulating jacksonian epilepsy. Chauffard¹ described a case in which the unilateral convulsions rapidly alternated from one side to the other. The occurrence of aphasia in such cases has been described by Osler,² whose attention was drawn to the existence of such phenomena by the early paper of Peabody.³ "Uremic" amaurosis is another symptom of the hypertensive encephalopathy which is not extremely rare, the nature of the blindness being disclosed by its association with hypertension, its

1 Chauffard. De l'urémie convulsive a form d'épilepsie jacksonienne, *Arch gen de med* 2 5, 1887.

2 Osler. Transient Attacks of Aphasia and Paralysis in States of High Blood Pressure and Arteriosclerosis, *Canad M A J* 1 919, 1911.

3 Peabody. Relations between Arterial Disease and Visceral Changes, *Tr A Am Phys* 6 170, 1891.

transitory nature, the negative ophthalmoscopic manifestations, apart from possible narrowing of the arteries, and the preservation of the light reflex which shows the cerebral origin. Various motor palsies, cerebral deafness, hemianopia and other focal cerebral symptoms of sudden onset and brief duration are vividly described in the accounts of "acute uremia" of the older authors, though in these descriptions what we here term the hypertensive encephalopathy and symptoms of uremia are indiscriminately mixed. The only symptom that we desire to discuss further here is headache, which is a frequent—we believe the most frequent—manifestation of the hypertensive encephalopathy. Its nature can often be recognized in the absence of other cerebral symptoms when it occurs as the culmination of a rapid rise in blood pressure, is unaccompanied by nitrogen retention and is relieved by venesection or lumbar puncture.

PATHOGENESIS

The postmortem examination of the brain of a patient who presented symptoms of the hypertensive encephalopathy does not reveal any focal lesions to account for the epileptiform convulsions, amaurosis, aphasia or other cerebral manifestations that were so striking during life. The brain is pale, usually almost bloodless. In some instances, the brain substance and meninges are edematous, but in others they do not show any evidence of edema and, in fact, may be unusually dry. In view of this paucity or absence of anatomic changes, it seems necessary to seek the pathogenesis of the hypertensive encephalopathy along "functional" lines. In this connection, two considerations are of paramount importance, namely, the relation of the hypertensive encephalopathy to disturbances of renal function and to arterial hypertension.

Renal Function—It has been known since the time of Christison⁴ that epileptiform convulsions and the other features of the hypertensive encephalopathy may occur in chronic interstitial nephritis without any diminution in the volume of urine, though in the majority of cases the seizures do occur during a period of oliguria. It is to Volhard⁵ that we are indebted for first demonstrating convincingly that what is here termed the hypertensive encephalopathy is not a consequence of impaired renal function. The application of modern methods of testing renal function (concentration test, dye excretion, etc.) shows that many patients presenting the typical hypertensive encephalopathy have no demonstrable impairment of renal function. Moreover, the blood chemistry is usually normal in all respects. Of course, the underlying kidney

⁴ Christison. On Granular Degeneration of the Kidneys, Edinburgh, 1839, p. 176.

⁵ Volhard, in Mohr and Stachelin's Handbuch der inneren Medizin, Berlin, 3 1346, 1918.

disease may cause a coincident impairment of renal function with its attendant changes in the blood chemistry, but the frequent occurrence of the hypertensive encephalopathy without renal insufficiency shows that there is no obligate connection between the two phenomena. On the other hand, the extreme rarity of symptoms of the hypertensive encephalopathy in the most typical impairment of renal excretion, that due to mechanical obstruction of the urinary passages, shows that retention of urinary constituents is not the cause of the hypertensive encephalopathy.

Similarly inadequate is the hypothesis of Widal,⁶ still widely held in France. He believed that the symptoms which we group together as the hypertensive encephalopathy are the results of chloride retention with consequent saturation of the nervous centers with chlorides, and terms them chloruremia. In most cases there is no evidence whatever of chloride retention, and in mechanical urinary obstruction in which enormous chloride retention may occur (the plasma sodium chloride in one case was more than 1,100 mg per hundred cubic centimeters) without any manifestations of the hypertensive encephalopathy.

It is to be emphasized that severe generalized convulsions, which are the most striking feature of the hypertensive encephalopathy, are rare in true uremia. In fifty-one consecutive cases of chronic interstitial nephritis with renal insufficiency and nitrogen retention, studied at the Mount Sinai Hospital, only two showed generalized convulsions, and in neither of these were they of the extreme severity seen in the hypertensive encephalopathy. In well marked true uremia, slight convulsive movements and particularly fibrillary twitchings are common, apparently being due to the lowered calcium content of the blood that follows on phosphate retention. However, these differ markedly from the generalized convulsions of the hypertensive encephalopathy, which are obviously of cerebral origin.

These considerations indicate that the term "acute uremia" is a misnomer when applied to the acute cerebral episode which we here call the hypertensive encephalopathy. The term acute uremia should be reserved for cases of true uremia of unusually abrupt onset, and it is important from a diagnostic, therapeutic and particularly from a prognostic standpoint to differentiate sharply between true uremia and hypertensive encephalopathy.

HYPERTENSION

The symptoms which are here grouped together as the hypertensive encephalopathy occur in the presence of arterial hypertension. In most cases, this increase of blood pressure is manifest and, in fact, is usually

6 Widal and Lemerle. Die diätetische Behandlung der Nierenentzündungen, *Ergebn d inn Med u Kinderh* 4 543, 1909

extreme. We have seen cases in children in which the existence of arterial hypertension was not immediately manifest, only subsequent observation proving such figures as 120/80 to be above the normal for the child. Moreover, in the presence of cardiac failure, the hypertension may not be manifest, though the peripheral conditions (vasoconstriction) for hypertension are present: we have seen a case of eclamptic convulsions with fatal outcome in which there was other evidence that cardiac insufficiency was the cause of the relatively low blood pressure.

The onset of the cerebral symptoms is often preceded by an additional rise above the already elevated level of blood pressure. This may occur quickly particularly in eclampsia gravidarum or more gradually over a period of several days as was evident several times in the case described. After the attack, there is usually a sharp drop in the blood pressure. Both these points are well illustrated in the accompanying chart. The premonitory rise in blood pressure usually affects both systolic and diastolic pressure. Sometimes the rise in the diastolic pressure is disproportionately great, perhaps indicating that the heart is unable to cope fully with the great increase in peripheral resistance.

The fact that a marked rise in blood pressure so often precedes the attack and that the cerebral phenomena often clearly form the culmination of the rise indicates clearly the intimate and probably causal relation of the rise in pressure to the cerebral syndrome.

The causal relation of the hypertension to the hypertensive encephalopathy is further indicated by certain facts concerning the occurrence of the identical cerebral syndrome in the three widely differing conditions of diffuse glomerulonephritis, toxemia of pregnancy and acute lead poisoning, facts which have long been known individually, but whose great importance for the pathogenesis of the cerebral syndrome has been emphasized only in recent years by Vaquez⁷, Pal⁸ and Volhard⁹.

In the toxemia of pregnancy the eclamptic seizure invariably occurs in the presence of arterial hypertension (Vaquez and Nobécourt)¹⁰. The classic form of the eclamptic attack consists in epileptiform seizures in every way analogous to those occurring in glomerulonephritis. The attacks can often be shown to follow an added rise in the blood pressure and to be followed by a drop. As in glomerulonephritis transitory amaurosis, aphasia, hemiplegia or other focal cerebral symptoms may be part of the syndrome. These may occur in the presence of intact renal

7. Vaquez: *Maladies du Cœur*, Paris 1921, p. 477.

8. Pal: *Gefässkranken*, Leipzig 1915.

9. Volhard: *Der arterielle Hochdruck*, Verhandl. d. deutsch. Gesellsch. f. inn. Med. 35:184, 1923.

10. Vaquez and Nobécourt: *De la pression artérielle dans l'éclampsie puerpérale*, Bull. et mém. Soc. méd. d. hôp. de Paris 14:117, 1897.

function At necropsy, cerebral anemia and often cerebral edema may be present, as has been demonstrated both post mortem and intra vitam (by trephining) by the exhaustive investigations of Zangemeister ¹¹

Lead encephalopathy is also always associated with arterial hypertension (Traube ¹² Vaquez ¹³) The convulsions are likewise epileptiform in character and may be similarly accompanied by transitory focal cerebral symptoms such as aphasia and amaurosis Renal function is often entirely intact, though there is usually oliguria during the attack The anatomic manifestations in the brain are the same as those in the other two conditions, consisting of anemia and sometimes edema (Tanquerel des Planches) ¹⁴

From this brief survey it is seen that the same group of transitory cerebral symptoms may occur in the three etiologically diverse conditions of diffuse glomerulonephritis, acute lead poisoning and the toxemia of pregnancy The cerebral syndrome cannot be due to renal failure in these conditions for in each of them the symptoms may occur in the presence of entirely intact renal function Each of the conditions is frequently marked by the occurrence of arterial hypertension, and it is only in the presence of hypertension that the cerebral symptoms present themselves It is therefore probable that the hypertension is causally connected with the cerebral syndrome What is the nature of the link between the hypertension and the cerebral syndrome? Two factors, cerebral vasoconstriction and cerebral edema, must be considered in this connection

Cerebral Vasoconstriction—All available evidence indicates that, whatever the ultimate causation may be, the immediate mechanism of arterial hypertension in glomerulonephritis is a widespread, and perhaps universal, peripheral vasoconstriction We have no precise information as to the extent to which individual vascular territories, and particularly those of the brain, are involved in the vasoconstriction But it has already been mentioned that at the autopsy of patients who had the symptoms of the hypertensive encephalopathy, the brain is usually found pale and the vessels devoid of blood, indicating that the vasoconstriction within the skull has been particularly marked

Other indirect evidence of vasoconstriction in the brain is sometimes furnished by ophthalmoscopic examination, for the retina ("the mirror of the brain") is an embryologic outgrowth of the brain and their blood supplies are closely interrelated Here it is usually possible to observe

11 Zangemeister Die Eklampsie eine Hirndruckfrage, Ztschr f Geburtsh u Gynak 79 124, 1916

12 Traube Gesammelte Beitrage zur Pathologie und Physiologie 2 551, 1871

13 Vaquez La tension arterielle dans le saturnisme aigu et chronique, Semaine méd 23 385, 1904

14 Tanquerel des Planches Traite des maladies de plomb, Paris 2 350, 1839

in patients with hypertensive encephalopathy that the retinal arteries are narrow, this was repeatedly noted in the case reported, before the actual albuminuric retinitis appeared. There are a number of observations on record in which blindness in acute hypertensive states has been shown by ophthalmoscopic observation to be the result of spastic closure of the retinal arteries, vision returning as the blood flow through these vessels was restored. Among those who have made such observations are Elschnig,¹⁵ Wagenmann¹⁶ and Smith.¹⁷ Labadie-Lagrave and Lauby¹⁸ observed a patient with acute lead poisoning who became almost completely blind when the blood pressure reached 250 mm of mercury. Vision returned when the blood pressure was lowered to 170 mm by the administration of amyl nitrite. An hour later the amaurosis recurred, to disappear as the blood pressure gradually fell to normal on the following day.

The most important evidence of the fundamental rôle played by angiospastic phenomena in the genesis of the hypertensive encephalopathy is furnished by the extreme suddenness with which the individual cerebral phenomena come and go, leaving no trace whatever behind them. Moreover, in the same case the focal cerebral symptoms often change. In the case described, the patient had aphasia with the first attack, then his convulsions began on the right side, and later they started on the left side. Sometimes they would affect only the face or an upper extremity, or there would be unilateral convulsions. Chauffard¹ saw a patient in whom the convulsions alternated many times during a day from one half of the body to the other. We are unable to explain such phenomena other than on a vasomotor basis.

Localized vascular spasms may occur in hypertensive patients in parts of the body other than the brain. The observations on the retina have already been mentioned. Not uncommon in hypertensive patients, though actually observed infrequently, is the so-called "phenomenon of the dead finger," first described by Dieulafoy¹⁹ as an initial symptom of uremia. Actually, the dead finger symptom has no relation to uremia but occurs in hypertensive patients whatever the state of renal function. It consists of a sudden feeling in one or more fingers or toes as though they were "dead." The patients may also note that the finger appears

15 Elschnig. Sehstörungen durch Bleivergiftung, Wien med Wchnschr **48** 1305, 1898.

16 Wagenmann. Beitrag zur Kenntnis der Zirkulationsstörungen in den Netzhautgefassen, Arch f Ophth **43** 219, 1897.

17 Smith. Intermittent Closure of Cerebral Arteries, Brit M J **2** 1380, 1909.

18 Labadie-Lagrave and Lauby. Accident aigu du saturnisme et hypertension, Tribune med **38** 437, 1906.

19 Dieulafoy. Text Book of Medicine, Translated by Collins and Liebmann, ed 2, New York, 1912, p 1112.

white The "dead" finger symptom passes away as quickly as it came, and even observant patients will usually tell about this phenomena only when questioned specifically Volhard⁹ believed that there is a strong element of cutaneous vasoconstriction in the production of the extreme pallor of many patients, which is out of all proportion to the anemia and in the absence of edema Lead colic appears only in the presence of arterial hypertension, and Vaquez⁷ adduced strong evidence that it is an ischemic pain due to vasoconstriction of the mesenteric vessels

Cerebral Edema—The theory that edema of the brain plays a part in the causation of "uremic" attacks was suggested by Owen Rees²⁰ and elaborated by Traube,¹² who believed the cerebral edema to result from the concomitance of arterial hypertension, which he recognized as always present in "uremia" and hydremia As a result of the combination of increased blood pressure and hydremia, fluid is pressed through the capillary walls Since the pressure in the aortic system is higher than that in the capillaries, these are compressed with resultant cerebral/anemia, the consequences of which are the convulsions, coma and other cerebral symptoms Traube's theory was discarded for a long time after Cohnheim²¹ showed that edema of the brain is most often absent in uremia, but has been resuscitated by Volhard⁹ for certain cases of what we here term the hypertensive encephalopathy In this country, strong evidence of the significance of edema of the brain for the causation of cerebral attacks in glomerulonephritis has recently been published by Blackfan²² Blackfan recognized clearly the nonuremic nature of the cerebral symptom which he believed due to edema of the brain, and suggested that they be termed the cerebral symptoms of acute glomerulonephritis

Edema of the brain is found in some but not in all patients who have had the symptoms of the hypertensive encephalopathy The edema may be so marked that on opening the calvarium the dura is found tensely stretched The convolutions are flattened and the sulci shallow There may be a conical deformation of the brain stem ("medullary cone"), showing that it has been pressed into the foramen magnum, this is well seen in an illustration by Blackfan The edema of the brain substance sometimes results in great narrowing of the ventricles (Tanquerel des Planches¹⁴), so that the latter appear as mere slits when the brain is hardened in situ (Volhard⁹) In other cases, the brain may be dry, as we have seen several times Such "dry" brains may be found despite

20 Rees On the Nature and Treatment of Diseases of the Kidney, London, 1850, p 67, quoted by Senator, *Krankheiten der Niere*, Vienna, 1902, p 96

21 Cohnheim *Vorlesungen über allgemeine Pathologie*, Berlin, 2 455, 1877-1880

22 Blackfan *Acute Nephritis in Children with Special Reference to the Treatment of Uremia*, Bull Johns Hopkins Hosp 39 69 (Aug) 1926

extreme anasarca of the skin. It has been claimed by Volhard⁵ and by others that failure to find edema of the brain at necropsy does not necessarily mean that it was absent during life. If this is so, it seems difficult to see why the edema should disappear in some cases and remain in others, and it must be concluded that failure to find edema of the brain at necropsy is strong evidence that it was not present in marked degree during life.

It is not clear how cerebral edema, when present, is produced. Of course, the mechanism suggested by Traube¹² is untenable, for we now know that most of the patients do not have hydremia. Moreover, arterial hypertension does not by any means necessarily indicate capillary hypertension and therefore would not be effective in forcing fluid from the capillaries. The cerebral edema in these cases is not merely part of a general edema, for the most widespread edema may be present (as in nephritis) without any cerebral edema, and conversely the cerebral edema may be marked without any edema elsewhere, as we have seen in eclampsia gravidarum. Volhard⁵ believed that cerebral edema in the hypertensive encephalopathy is due to ischemic injury of the capillaries of the brain resulting from arteriolar constriction. There can be little doubt that the cerebral edema in these cases is the result of the phenomena producing the hypertension, for it occurs only in the presence of the latter, but we do not know the precise nature of the relationship. We are unable to agree with Blackfan's view that the edema of the brain causes, through medullary compression, the rise in blood pressure, for the latter is present before the onset of the cerebral symptoms and even the "extra rise" preceding the cerebral attack may come on gradually during a week or more, as was illustrated several times in the foregoing case. It is hard to conceive of the cerebral edema as producing through medullary compression an elevation of blood pressure as its sole symptom.

The group of symptoms here termed the hypertensive encephalopathy was subdivided by Volhard⁵ in his original description into two pathogenetically distinct parts, acute and chronic false uremia. In acute false uremia, he considered the symptoms due to cerebral edema, in chronic false uremia, to cerebral angiospasm. We do not believe that such a division can be carried out, for the primary pathogenetic factor in all the cases is the cerebral anemia resulting from arteriolar constriction, the edema being one of the consequences of the ischemia. In turn, the edema also produces symptoms in some cases, but this is secondary. The attacks which come and go as quickly as did the individual seizures in the case described are evidently the direct results of the cerebral vasoconstriction. However, we have seen that these attacks may be frequently repeated over a long period of time so as to give a "chronic" picture despite the fact that at no time is there evidence of edema of the

brain As is well known from postmortem observations, a considerable degree of cerebral edema may be present without causing any symptoms; but in those cases of hypertensive encephalopathy in which the cerebral symptoms present for a considerable time a picture simulating that of tumor of the brain with severe headache, cerebral vomiting, perhaps convulsions or focal cerebral symptoms with a high pressure of the cerebrospinal fluid and well marked choked disks (in one of our cases more than 5 diopters), it is probable that there is marked edema of the brain Such cases are seen particularly in the toxemia of pregnancy and in children with glomerulonephritis However, moderate papilledema or increased pressure of the cerebrospinal fluid in themselves do not necessarily indicate edema of the brain in a hypertensive patient The papilledema may be the initial phase of albuminuric retinitis, as is not at all uncommon, and may have no relation to increased intracranial tension And it is not uncommon to find long continued moderate elevation of the subarachnoid pressure in hypertensive patients, though no other evidence of edema of the brain develops and none is found at necropsy

There does not seem to be any convincing evidence that edema of the brain, in itself and in the absence of arterial hypertension, can produce the picture of the hypertensive encephalopathy in nephrosis Volhard² mentioned a case said to have been observed by another, but does not seem to have seen one himself

From all available evidence, the cerebral syndrome here called the hypertensive encephalopathy has as its essential cause arterial hypertension, edema of the brain being only inconstantly present as a result of the hypertension though it may when present, contribute essentially to the clinical picture We do not know why the hypertensive encephalopathy complicates only certain varieties of hypertension—those found in glomerulonephritis the toxemia of pregnancy and lead poisoning—but does not occur in so-called essential hypertension It will be noted that the varieties of hypertension in which the hypertensive encephalopathy occurs are those in which the hypertension often arises, or is increased suddenly while in essential hypertension the increased blood pressure usually sets in gradually We do not know whether this difference is significant for the pathogenesis of the hypertensive encephalopathy The mechanism of the cerebral vasoconstriction in these cases is as dark as that of the hypertension itself Vaquez³ believed the vasoconstriction to be due to epinephrine, but this is no more proved than his epinephrine theory of hypertension In the cases of lead poisoning, the vascular contraction is presumably due to the action of the lead on the vessels and in the toxemia of pregnancy to the hypothetical

eclampsia toxin Foster ²³ claimed to have isolated a crystalline base that produces convulsions from the blood of nephritic patients with convulsions, but this interesting investigation, so far as we know, has never been confirmed. The genesis of the cerebral vasoconstriction, like that of the antecedent vasoconstriction, must as yet be considered as completely unexplained.

That cerebral anemia can produce epileptiform convulsions has been known since the classic experiments of Kussmaul and Tenner ²⁴. They were able to produce immediate epileptiform convulsions in the rabbit by ligating the arteries to the head. Immediately after the ligature was released, the convulsions ceased. Recently, it has been shown by Dandy ²⁵ that clonic convulsions can be produced only by stimulating the motor cortex, and no other cortical or subcortical regions, consequently, the motor cortex must be involved in the cases showing epileptiform convulsions.

SUMMARY

The acute cerebral episodes of diffuse glomerulonephritis, the toxemia of pregnancy and acute lead poisoning are symptomatically identical, consisting of such symptoms as epileptiform convulsions, coma, violent headache, cerebral vomiting and such focal cerebral symptoms as aphasia, amaurosis and hemiplegia.

These cerebral episodes occur only in patients with arterial hypertension and are generally preceded by an additional rise in blood pressure above the previous high level. For this reason, the term hypertensive encephalopathy is proposed for the acute cerebral episodes occurring in hypertensive states.

The hypertensive encephalopathy is not the result of impaired renal function, so the term acute uremia is a misnomer.

Available evidence indicates strongly that the hypertensive encephalopathy is the result of cerebral anemia produced by cerebral vasoconstriction. The cerebral edema which is present in some, but not in all, of the cases is secondary to the vasoconstriction, though the exact mechanism of the connection is not clear. While the cerebral edema produces symptoms in some cases, it is not the essential cause of the hypertensive encephalopathy.

23 Foster. Uremia, Harvey Lectures **16** 52, 1920-1921.

24 Kussmaul and Tenner. Epileptiform Convulsions from Hemorrhage, New Sydenham Society, London, 1859.

25 Dandy. Experimental Investigation of Convulsions, J. A. M. A. **88** 90 (Jan. 8) 1927.

A case of recurrent hypertensive encephalopathy is described in which the cerebral episodes were repeated many times and in varying forms over a period of twenty months

Generalized convulsions are rarely a symptom of true uremia, having occurred in only two of fifty-one cases of chronic interstitial nephritis showing nitrogen retention

INFLUENCE OF POSTURE ON PHENOLSULPHON- PHTHALEIN TEST FOR KIDNEY FUNCTION ¹

NARCISO CORDERO, M D

AND

MAURICE H FRIEDMAN, S B

CHICAGO

Studies on the so-called functional albuminuria, also variously designated as cyclic, intermittent, physiologic, orthostatic, etc, first focused attention on posture as a factor in renal activity. Naturally, the criterion most often used in the earlier works on this subject was the appearance of albumin in the urine. The volume of urine excreted in different body postures had been recorded by some investigators only as subsidiary observations. Edel ¹ noted decreased urine volume during the standing posture coincident with the maximum albuminuria and, conversely, an increased volume on the assuming of a recumbent posture when albumin disappeared from the urine. Linnoisier and Lemoine ² studied the influence of posture on renal activity by making twelve hour observations on renal and albuminuric patients. Notwithstanding the lack of adequate control of diet and water intake, they could observe a definite decrease, not only of the urine, but of urea and chlorides, during standing, as compared with the urine collected while the subjects were in bed. They also ³ found that the excretion of potassium iodide and of methylene blue was distinctly lowered when the patient was in the standing posture, and called attention to this factor in connection with the renal function tests in vogue at the time. These authors thought that the decreased secretion in the upright position was due to "torsion of the renal pedicle" brought about by a slight descent of the kidneys due to gravity. In support of this theory they point out ⁴ that in pregnant women a reverse relationship obtains, namely, increased renal activity on standing and decreased on lying down, the weight of the gravid uterus compressing kidney and pedicle more in the recumbent than in the erect position. Their data on this point are meager, and, as they themselves admit, this relationship is not constant.

Since the general adoption of the better and quicker method of testing renal function introduced by Rowntree and Geraghty,⁵ little or no

* From the Physiology Laboratory of the University of Chicago

1 Edel Munchen med Wchnschr **48** 1833, 1901

2 Linnoisier and Lemoine Compt rend Soc de biol **55** 466, 1903

3 Linnoisier and Lemoine Compt rend Soc de biol **55** 605, 1903

4 Linnoisier and Lemoine Compt rend Soc de biol **58** 691, 1903

5 Rowntree and Geraghty J Pharmacol & Exper Therap **1** 579, 1910

attention has been given to posture as a possible modifying factor. In 1916 Barker and Smith⁶ reported phenolsulphonphthalein tests on six patients with orthostatic albuminuria, but were able to test the influence of posture on only two of them. One patient (case 1) showed a distinct increased phenolsulphonphthalein excretion in the recumbent posture over that in the upright position. The other patient (case 6) did not show any change. Nørgaard,⁷ using a modification of the Strauss water test in twelve cases of orthostatic albuminuria found much reduced elimination of water and chloride during four hours of standing as compared with the elimination in similar periods of recumbency.

While considerable work has been done on patients with orthostatic albuminuria, little has been done to test the influence of changes of posture in renal activity on normal persons. Recently, White, Rosen, et al.,⁸ in a series of well controlled experiments on normal persons, proved conclusively that renal activity, as a whole, is increased in the recumbent posture as judged by the greater elimination of water and solids, except ammonia, when compared to that in standing.

The present studies were undertaken to determine the influence of posture on the phenolsulphonphthalein renal function test to see whether such an influence manifests itself, and if so, to what extent in normal persons. It was felt that such data would be useful in interpreting the results in pathologic cases and might suggest new aids to differential diagnosis.

PROCEDURE

The experiments were made on two healthy laboratory workers, with neither symptoms nor previous history of impaired kidney function. The intake of food and water on the night preceding the experiment was not rigidly controlled save for the usual habits of the person. On the following morning, however, the subjects partook of a standard breakfast which excluded tea, coffee and water.

The tests were carried out as follows. 1 cc of a solution containing 6 mg of phenolsulphonphthalein was injected subcutaneously. The bladder was emptied, a definite quantity of water was taken by mouth, and the subject was made to lie quietly in bed for two hours. During this period hourly samples of urine were collected, their volumes were measured and the amount of dye eliminated was determined colorimetrically in the usual way. At the end of the two hours a second subcutaneous injection of the same amount of dye was administered, the same quantity of water was drunk, and the subject changed to the standing position for another two hours, avoiding muscular exertion as much as possible. Samples of urine were collected hourly and examined as before. Or, conversely with the same general procedure, the subject started the experiment in the standing posture and ended in the recumbent. Most of the control procedures were carried out in essentially the same manner as the fore-

6 Barker and Smith. *Am J M Sc* **151** 44, 1916

7 Nørgaard. *Acta med Scandinav* **8** 304, 1923

8 White, Rosen et al. *Am J Physiol* **78** 185, 1926

going except that instead of the posture being changed during the last two hours the subject continued in the same posture he started with. A few control experiments were carried out along these same lines but with only one subcutaneous injection of 6 mg of the dye. This type of control was subsequently abandoned as being of little value for the purpose in view.

At first, the intake of water during the experiment was fixed at 200 cc per two hours, taken immediately after the injection of the dye. Due to the difficulty experienced by one subject (M H F) in voiding small quantities of urine, it was decided to increase the water intake in both subjects and to give the water in two doses. As a result, M H F, the larger of the two, received in the later experiments 300 cc at the time of injection, and 200 cc at the beginning of the second hour of each two hour period. Similarly, N C received 200 cc and 100 cc for each two hour period. In this manner we could assure a fairly uniform diuresis throughout the two successive two hour periods, without gastric discomfort.

From time to time the urines were tested for albumin. One subject, N C, was able to urinate every thirty seconds. In this person the first appearance of the dye in the urine was observed from time to time. From the constantly negative albumin tests and the unchanged first appearance time of the dye, together with the complete absence of any abnormal subjective feelings we feel reasonably certain that our results were obtained from kidneys that remained normal throughout the rather long series of injections.

RESULTS

Table 1 represents the results on N C and M H F, grouped according to the type of procedure followed.

| | |
|-------------------|---|
| Group A, R_1S_2 | } = two injections, one at the start, another after two hours |
| Group B, S_1R_2 | |
| Group C, R_1R_2 | |
| Group D, S_1S_2 | |
| Group E, R_1R_2 | } Only one initial injection |
| Group F, S_1S_2 | |

R stands for recumbent, S, for standing. The number following the letter indicates 1, the first two hours, 2, the last two hours. All the figures for excretion are totals for two hour periods.

For convenience of expression the 6 mg of phenolsulphonphthalein injected has been designated 100 units. This enables us to distinguish the actual quantity excreted from the percentage elimination, especially in dealing with the percentage elimination of the last two hours, in which we have to reckon with a residue from the previous two hour period. There is no way of estimating accurately the amount of this residue. A certain portion of the dye is excreted through other channels, and some may be destroyed in the body. These are, however, relatively small quantities for two hours, compared with that eliminated through the kidneys. By subtracting the elimination of the first two hours from the 100 units injected at the start, we get a figure which is our closest approach to the quantity of this residue. The number of

TABLE 1—Results of Tests to Determine Influence of Posture on Renal Function

EXPERIMENTS ON N C

| Exp | Recumbent first 2 hours (R ₁) | | | Standing last two hours (S ₁) | | | |
|------|---|--------|----------|---|-------------------------|--------|--------|
| | Dye | | Water Cc | Units in Body * | Water Cc | | |
| | Elimination per Cent | Intake | Output | | Elimination per Cent | Intake | Output |
| 1 | 66.1 | 200 | 73 | 133.9 | 43.2 | 200 | 79 |
| 2 | 74.4 | 200 | 350 | 125.6 | 38.1 | 200 | 232 |
| 21 | 44.0 | 300 | 373 | 156.0 | 39.2 | 300 | 372 |
| A 25 | 71.4 | 300 | 353 | 128.6 | 41.4 | 300 | 282 |
| 29 | 43.4 | 300 | 452 | 156.8 | 37.8 | 300 | 310 |
| 48 | 61.9 | 300 | 241 | 138.1 | 51.1 | 300 | 341 |
| 52 | 62.7 | 300 | 480 | 137.3 | 56.8 | 300 | 309 |
| 3 | Standing first 2 hours (S ₁) | | | Recumbent last 2 hours (R ₁) | | | |
| 4 | 43.7 | 200 | 125 | 156.3 | 50.2 | 200 | 576 |
| 23 | 46.6 | 200 | 155 | 153.4 | 39.5 | 200 | 369 |
| B 27 | 44.0 | 300 | 207 | 156.0 | 46.4 | 300 | 752 |
| 38 | 40.0 | 300 | 69 | 160.0 | 46.3 | 300 | 491 |
| 46 | 51.5 | 300 | 89 | 148.5 | 54.3 | 300 | 490 |
| 54 | 47.1 | 300 | 157 | 152.9 | 58.7 | 300 | 555 |
| 33 | 52.0 | 300 | 48 | 148.0 | 62.3 | 300 | 675 |
| C 36 | Recumbent first 2 hours (R ₁) | | | Recumbent last 2 hours (R ₂) | | | |
| 42 | 60.7 | 300 | 205 | 139.3 | 49.2 | 300 | 731 |
| 50 | 56.4 | 300 | 210 | 143.6 | 53.9 | 300 | 712 |
| 30 | 55.2 | 300 | 265 | 144.8 | 53.9 | 300 | 751 |
| D 31 | 57.5 | 300 | 168 | 142.5 | 49.4 | 300 | 750 |
| 40 | Standing first 2 hours (S ₁) | | | Standing last two hours (S ₂) | | | |
| 44 | 46.0 | 300 | 117 | 154.0 | 47.8 | 300 | 392 |
| 56 | 45.0 | 300 | 118 | 155.0 | 40.0 | 300 | 392 |
| F 11 | 57.9 | 300 | 172 | 142.1 | 52.1 | 200 | 210 |
| 13 | 57.1 | 300 | 160 | 142.9 | 54.7 | 300 | 463 |
| 16 | 63.6 | none | 93 | 136.4 | 62.9 | none | 60 |
| 11 | Recumbent first 2 hours (R ₁) | | | Recumbent last 2 hours (R ₂) | | | |
| 13 | 32.7 | 500 | 604 | 67.3 | 23.9 | 150 | 590 |
| F 16 | 34.1 | 500 | 550 | 65.9 | 18.5 | 200 | 670 |
| 9 | 51.3 | 500 | 539 | 48.7 | 36.9 | 200 | 581 |
| F 14 | Standing first 2 hours (S ₁) | | | Standing last two hours (S ₂) | | | |
| 18 | 49.3 | 500 | 228 | 50.7 | 21.3 | 200 | 311 |
| | 53.9 | 300 | 65 | 46.1 | 35.7 | 300 | 233 |
| | 56.2 | 500 | 282 | 43.8 | 26.7 | 200 | 263 |

EXPERIMENTS ON M H F

| Exp | Recumbent first 2 hours (R ₁) | | | Standing last two hours (S ₂) | | | |
|------|---|--------|----------|--|-------------------------|--------|--------|
| | Dye | | Water Cc | Units in Body * | Water Cc | | |
| | Elimination per Cent | Intake | Output | | Elimination per Cent | Intake | Output |
| 5 | 78.9 | 400 | 517 | 121.1 | 60.0 | 400 | 115 |
| 7 | 59.3 | 400 | 515 | 140.7 | 41.2 | 400 | 106 |
| 24 | 66.8 | 500 | 524 | 133.2 | 57.9 | 500 | 210 |
| A 28 | 93.0 | 500 | 560 | 107.0 | 69.2 | 500 | 168 |
| 39 | 65.4 | 500 | 385 | 134.6 | 44.8 | 500 | 233 |
| 47 | 63.9 | 500 | 572 | 136.1 | 61.2 | 500 | 226 |
| 55 | 71.1 | 500 | 540 | 128.9 | 60.7 | 500 | 128 |
| 6 | Standing first 2 hours (S ₁) | | | Recumbent last 2 hours (R ₂) | | | |
| 8 | 48.5 | 400 | 271 | 151.5 | 44.1 | 400 | 868 |
| 22 | 47.0 | 400 | 245 | 159.3 | 50.7 | 400 | 580 |
| B 26 | 86.0 | 500 | 125 | 114.0 | 71.1 | 500 | 910 |
| 49 | 72.9 | 500 | 117 | 127.1 | 56.6 | 500 | 921 |
| 53 | 63.2 | 500 | 139 | 136.8 | 70.1 | 500 | 794 |
| 57 | 62.9 | 500 | 115 | 137.1 | 61.9 | 500 | 694 |
| 32 | 73.2 | 500 | 67 | 126.8 | 76.7 | 500 | 771 |
| C 35 | Recumbent first 2 hours (R ₁) | | | Recumbent last 2 hours (R ₂) | | | |
| 41 | 64.9 | 500 | 434 | 135.1 | 66.0 | 500 | 801 |
| 45 | 63.1 | 500 | 456 | 136.9 | 59.3 | 500 | 763 |
| 34 | 81.5 | 500 | 423 | 118.5 | 74.1 | 300 | 588 |
| D 37 | 67.9 | 300 | 890 | 132.1 | 69.5 | 500 | 611 |
| 43 | Standing first 2 hours (S ₁) | | | Standing last two hours (S ₂) | | | |
| 51 | 60.4 | 500 | 368 | 139.6 | 52.2 | 500 | 414 |
| E 12 | 56.7 | 500 | 54 | 143.3 | 61.2 | 500 | 66 |
| 15 | 70.3 | 500 | 110 | 129.7 | 70.8 | 500 | 484 |
| 19 | 61.5 | 500 | 220 | 138.5 | 60.7 | 500 | 237 |
| 10 | Recumbent first 2 hours (R ₁) | | | Recumbent last two hours (R ₂) | | | |
| F 17 | 57.7 | 700 | 547 | 42.3 | 30.9 | 200 | 317 |
| 20 | 74.4 | 700 | 443 | 25.6 | 30.4 | 400 | 668 |
| | 77.7 | 700 | 393 | 22.3 | 40.3 | 400 | 629 |
| | Standing first 2 hours (S ₁) | | | Standing last 2 hours (S ₂) | | | |
| | 47.7 | 700 | 220 | 52.3 | 32.3 | 400 | 197 |
| | 67.5 | 700 | 428 | 32.5 | 59.0 | 400 | 179 |
| | 60.0 | 700 | 450 | 40.0 | 43.5 | 400 | 160 |

* These columns include the amount of dye left presumably from the previous injection plus the quantity given in the second injection, when this has been done. All figures for dye and water elimination are for two hour periods.

units of this probable residue plus the 100 units injected at the beginning of the last two hour period gives the figures given under the column "units in body," from which the percentage elimination of the last two hours is calculated. Considering that the destruction of the dye in the body and the elimination through extrarenal channels are comparatively small, and that these factors operate in every case at equal periods of time, namely, two hours, we feel that our calculation of this residue, though not exact, is accurate enough for comparative purposes.

In spite of variations in individual figures, the results indicate a definite though not marked increase in dye elimination in the recumbent posture, amounting in two hours with the quantities used, to about 10 to 13 per cent of the excretion of the erect position. This tendency

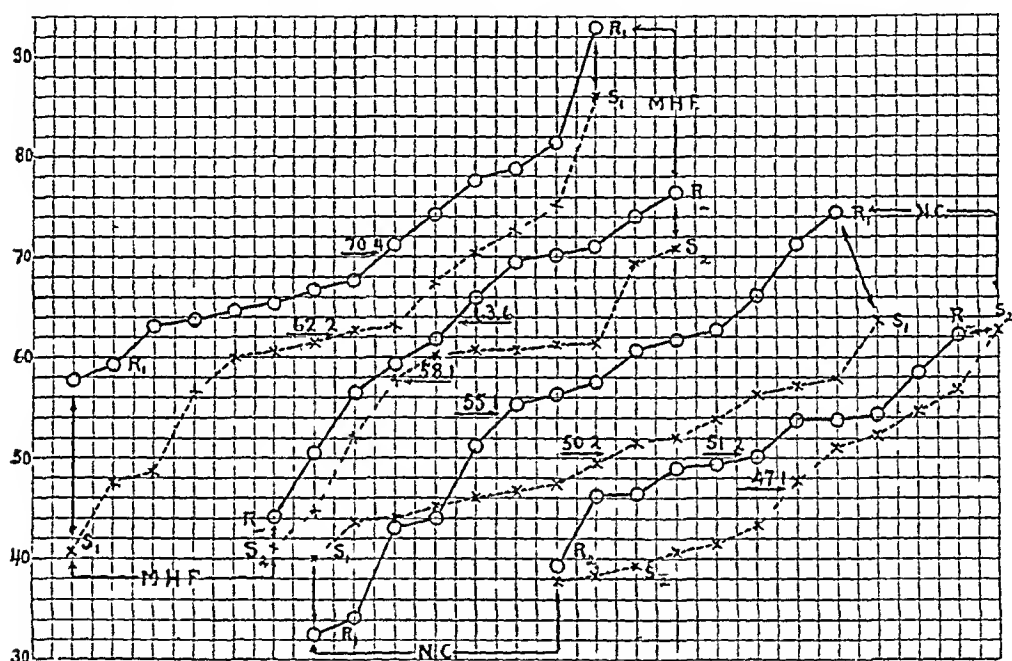


Fig 1—Influence of posture on phenolsulphonphthalein elimination. R_1 indicates recumbent first two hours, R_2 , recumbent last two hours. S_1 , standing first two hours, S_2 , standing last two hours, ordinates, percentage elimination, abscissas, individual results arranged in order of increasing magnitude.

is manifest with the various criteria used in evaluating the results. More striking is the effect on the volume of urine of the recumbent posture, showing an increase of more than 100 per cent over that of the two hour standing period.

ANALYSIS OF DATA

Phenolsulphonphthalein Excretion—Several ways of comparing the dye elimination (table 1) are possible.

1. Comparison of R_1 , the two hour elimination following the first injection in the recumbent posture, with S_1 , the two hour elimination

following the first injection in the erect posture, in the experiments of all groups

2 Comparison of R_2 , the percentage of elimination following the second injection in recumbency, with S_2 , the percentage elimination following the second injection while standing, in the experiments of groups *A*, *B*, *C* and *D*

Chart 1 represents graphically the foregoing comparisons for N C and M H F. The ordinates represent percentage elimination, and the abscissas, the individual results arranged in order of increasing magnitude. The elimination during the recumbent posture was distinctly higher than that during standing. Two extremely low recum-

TABLE 2—Comparison of Percentage Elimination During Successive Two Hour Periods on the Same Day~

| Subject | Group A S_2-R_1 | Group C (Control) R_2-R_1 | Group B R_2-S_1 | Group D (Control) S_2-S_1 |
|-----------------------------------|-------------------|--------------------------------|-------------------|--------------------------------|
| N C | -22.9 | -11.5 | +6.5 | +1.8 |
| | -30.3 | -2.5 | -7.1 | -4.1 |
| | -4.8 | -1.3 | +2.4 | -5.8 |
| | -30.0 | -8.1 | +6.3 | -2.4 |
| | -5.6 | | +2.8 | -0.7 |
| | -10.8 | | +11.6 | |
| | -5.9 | | +10.3 | |
| | | | | |
| Mean | -16.6 | -5.8 | +4.7 | -2.2 |
| Attributable to change of posture | | -10.8 | | +6.9 |
| M H F | -18.9 | +1.1 | -4.4 | -8.2 |
| | -18.1 | -3.8 | +10.0 | +4.5 |
| | -8.9 | -7.4 | -14.9 | +0.5 |
| | -23.8 | +1.6 | -16.3 | -0.8 |
| | -20.6 | | +6.9 | |
| | -2.7 | | -1.0 | |
| | -10.4 | | +3.5 | |
| | | | | |
| Mean | -14.8 | -2.1 | -2.3 | -1.0 |
| Attributable to change of posture | | -12.7 | | none |

* Taken from the experiments of groups A, B, C and D, table 1

* The figures indicate how much more (+) or less (-) is the excretion of the first two hour period than that of the second two hour period

bent figures for N C fall distinctly below the lower limits of the standing elimination. The subject had a severe cold, slight headache and general malaise at the time of those tests. Similar low values were never again encountered in the whole series. These two results may thus be discarded. Yet, even including them in the series under the consideration, the average of the recumbent figures is distinctly higher. Chart 1 also brings out the fact that the percentage of excretion during the first two hours, as well as during the last two hours, was decidedly greater in M H F than in N C, a fact which will perhaps not be brought out by a few isolated tests. Likewise, the recumbent increase of elimination over the standing was greater in M H F.

3 Comparison of the four hour elimination in recumbency and standing following one injection of the dye. Groups *E* and *F*, which

fall under this category, indicate increased recumbent excretion for M H F but not for N C. In the latter case, however, two of the three recumbent tests are the exceptionally low values mentioned previously. For the experiments on N C, therefore, this criterion is indecisive.

4. Comparison of the percentage of elimination during standing and during recumbency on the same day. From table 3 it is apparent that the dye elimination in the second of successive two hour periods was usually a little less than that of the first period, if the posture remained unchanged (experiments of groups C and D). When the posture was changed from the recumbent to the erect, the elimination during the second period was more markedly decreased. This was true in both N C and M H F (experiments of group A). When, however, the change was made from the erect to the recumbent posture, only in

TABLE 3—*Four Hour Output of Urine*

| Subject | Recumbent | | | Standing | | |
|---------|------------|------------|-------------------|------------|------------|-------------------|
| | Intake, Cc | Output, Cc | | Intake, Cc | Output, Cc | |
| | | Actual | per 100 Cc Intake | | Actual | per 100 Cc Intake |
| N C | 600 | 936 | 156 | 600 | 509 | 85 |
| | 600 | 922 | 153 | 600 | 510 | 85 |
| | 600 | 1,016 | 169 | 500 | 382 | 76 |
| | 600 | 918 | 153 | 600 | 623 | 104 |
| | 650 | 1,194 | 183 | 700 | 539 | 77 |
| | 700 | 1,250 | 178 | 600 | 293 | 49 |
| | 700 | 1,120 | 160 | 700 | 548 | 78 |
| | 1,000 | 1,235 | 123 | 1,000 | 782 | 78 |
| M H F | 1,000 | 1,219 | 122 | 1,000 | 120 | 12 |
| | 800 | 1,011 | 126 | 1,000 | 594 | 59 |
| | 1,000 | 1,501 | 150 | 1,000 | 457 | 46 |
| | 900 | 864 | 96 | 1,100 | 417 | 38 |
| | 1,100 | 1,111 | 101 | 1,100 | 617 | 56 |
| | 1,100 | 1,022 | 93 | 1,100 | 610 | 55 |
| | | | | | | |
| | | | | | | |

N C was there a definite increase in elimination. This will be referred to later.

Elimination of Water—Water, unlike phenolsulphonphthalein, is necessary in the body economy and behaves like a threshold substance. Since body water balance is generally constant, water excretion is proportional to the intake, other things being equal, and for the relatively short periods of observation made in the present experiments, the elimination at any particular period was also influenced by the excretion of the previous periods. The room temperature did not vary more than 3 C from day to day during the seven months covered by these experiments, so the variations in excretion of water through the kidneys due to this factor may be neglected.

1. Comparison of the output of the first two hours in one posture with that of the first two hours in another posture. Chart 2 represents such a comparison taken from all the groups of experiments in table 1. The ordinates give the volume of excretion per hundred cubic centi-

meters of intake, and the abscissas are the individual results arranged in order of magnitude. The increased volumes in recumbency are striking and consistent.

2. Comparison of the total output in the experiments of groups C, D, E and F in which one posture was kept for four hours. Recumbency increased the output from 50 to 200 per cent of the volume during standing, as may be readily seen from table 3.

3. Comparison of volumes of urine of two successive two hour periods on the same day. When one posture was maintained through the two successive periods, the urine volume of the second period was

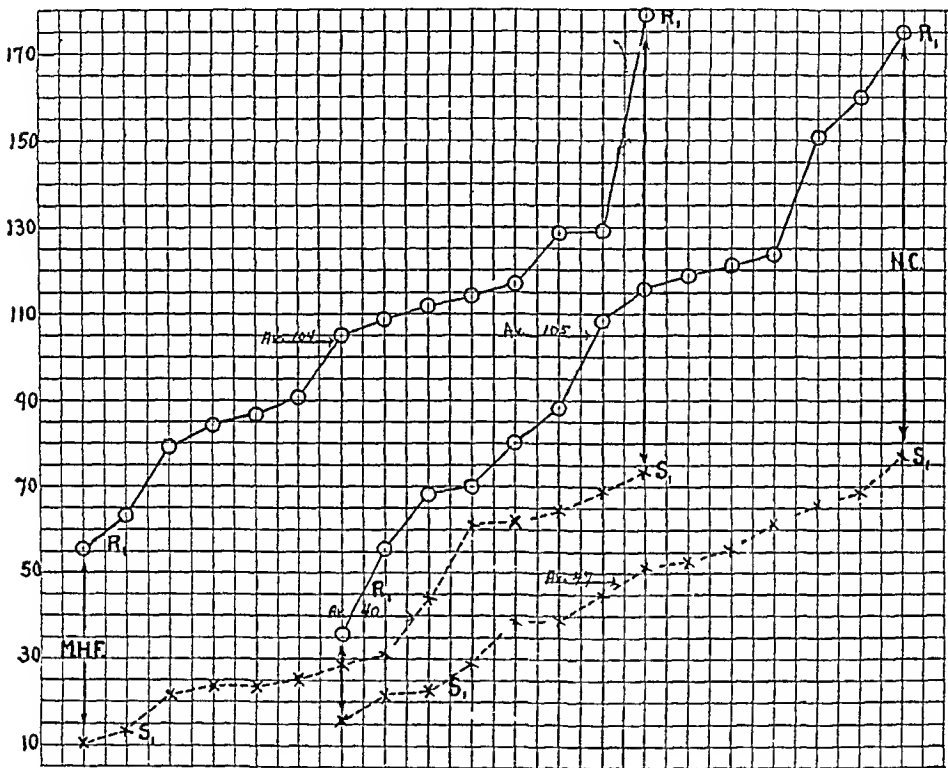


Fig 2—Influence of posture on urine output. R₁ indicates recumbent first two hours, S₁, standing first two hours, ordinates, volume per hundred cubic centimeters intake, abscissas, individual results arranged in order of increasing volumes.

a little greater than that of the first. A change from the recumbent to the erect posture effected a striking decrease in volume of urine (table 4). Conversely, a change from the erect to the prone position effects a significant increase in volume.

Volume of Urine and Excretion of Dye—Rowntree and Geraghty⁵ stated that the elimination of phenolsulphonphthalein was independent of the volume of output of urine. Snowden,⁹ however, in 1921 reported

9 Snowden Arch Int Med 28 603, 1921

that for diseased kidneys the percentage of dye eliminated ran fairly parallel with the volume of the urine. Similarly, Lundsgaard and Moeller,¹⁰ on patients with cardiac disease but no albuminuria, observed that with extremely low volumes of the urine the elimination of dye was also decreased.

Although such low volumes (10 cc or less) as those reported by Lundsgaard and Moeller were never encountered by us, our data disclose absolutely no correlation between the volume of urine and the elimination of dye. It may be reasonable to assume that the damaged renal cells of nephritic patients are less able to work with small volumes than normal cells. Yet, it is difficult to disregard the possibility

TABLE 4—*Comparison of Volumes of Urine Per Hundred Cubic Centimeters Intake of Two Successive Two Hour Periods on the Same Day**

| | Group A S ₂ —R | Group C (Control) R ₂ —R ₁ | Group B R ₂ —S | Group D (Control) S ₂ —S ₁ |
|--------------------------------------|------------------------------|--|--------------------------------|--|
| N C | + 3 | +175 | +225 | + 91 |
| | -59 | +167 | +107 | + 91 |
| | 0 | +162 | +182 | + 48 |
| | -21 | +191 | +141 | +101 |
| | -47 | | +133 | |
| | +34 | | +133 | |
| | -57 | | +209 | |
| Average | -21.5 | +174.5 | +147 | + 83 |
| Effect of change to standing posture | | -196 | Effect of change to recumbency | +64 |
| M H F | -100 | + 73 | +149 | +10 |
| | -103 | + 61 | + 84 | + 2 |
| | -63 | +112 | +157 | +75 |
| | -78 | - 36 | +161 | + 3 |
| | -70 | | +131 | |
| | -67 | | +116 | |
| | -82 | | +141 | |
| Average | -80.5 | + 47.5 | +134 | +22.5 |
| Effect of change to standing posture | | -128.0 | Effect of change to recumbency | +111.5 |

* The figures represent the increase (+) or decrease (—) in volume of the second two hour period as compared with that of the first two hour period. The subnumerals 1 and 2, following R or S, denote the first and second two hour periods respectively.

that the conditions giving rise to reduced excretion of dye concomitantly cause reduction of volume of output, and that the reduced volume and excretion of dye, though often coexistent, do not necessarily depend on each other unless extremely low volumes are encountered.

Demerits of the Subcutaneous Injection—The current practice in the application of the phenolsulphonphthalein test for renal function is to employ the intravenous route. Unquestionably when this method is followed one variable is eliminated. In fact when we examine the data on the use of the intravenous method we are struck at once, not only by the uniformity, but by the higher percentages of the elimination of the first hour. While these data have remained more or less unchallenged, the following facts have been generally overlooked:

Most of the data purporting to show the advantages of the intravenous route consist of one test on different persons, and emphasize especially the first hour elimination. There are only a few instances in which more than three or four tests have been made on the same person, either by the subcutaneous or by the intravenous route alone.

By arranging our data in chronological order we noted several groups of from two to five successive experiments in which the two hour excretion of dye was remarkably constant, being well within a variation of 10 per cent. It is possible that the five or six experiments on the same person which are offered as evidence of the reliability of the intravenous route are such a group as we have encountered, especially if the series of experiments is done within a short interval, when the circulation, diet, water intake and general body condition are fairly constant. Certainly, so few experiments do not permit a statement as to the reliability of any particular technic.

Sugimura and Aomura¹¹ studied the excretion of phenolsulphonphthalein on twenty-four healthy subjects, using different routes of

TABLE 5—Taken from Sugimura and Aomura

| Mode of Injection | Two Hour Percentage Excretion | | |
|---------------------------------|-------------------------------|--------|------|
| | Highest | Lowest | Mean |
| Subcutaneous | 63.4 | 39.0 | 58.4 |
| Intramuscular | 79.8 | 41.0 | 61.2 |
| Intravenous (with water intake) | 84.7 | 43.0 | 72.6 |
| (without water intake) | 79.3 | 43.0 | 68.2 |

injection on each. From table 4 of their paper we calculated the two hour excretions with the different methods of injection used and found the following:

Sugimura and Aomura point out the advantages of the intravenous route in the following terms: "Die Ausscheidung Kurve erreicht dabei schon in der ersten halben Stunde ihren Kulminationspunkt um in der zweiten halben Stunde wieder steil abzufallen. Bei subkutaner und intramuskulärer Injektion zeigen sich die Kurven als mehr inkonstant." In other words, emphasis is again given to the first hour. From the foregoing recalculated two hour table, the higher values for intravenous injection are evident, but it is also clear that as to the question of variability, one method of injection shows as much lack of uniformity as another.

Apparently, then, when the two hour excretions are taken into account the subcutaneous method of administration is not consistently more variable than the other methods. The multiplicity of factors capable of affecting the results makes one or two tests of little value in

11 Sugimura and Aomura. *Iohoku J Exper Med* 7 125, 1926

medical cases The subcutaneous route will permit as many determinations as necessary on the same patient, provided edema is not present Our data, we believe, adds one more evidence to the already well known harmlessness of phenolsulphonphthalein, even with prolonged use Furthermore, there is no evidence of development of any form of increased storage or increased destruction in the body

INTERPRETATION

The variability of results even on the same subjects will always detract from the value of any small series of experiments of this nature But our analysis of twenty-eight experiments on each of two subjects convinces us that there is a definite though not marked increase of from 10 to 13 per cent in the two hour elimination of phenolsulphonphthalein in the recumbent position as compared with that in standing Our belief is strengthened, furthermore, by the fact that the degree of difference is always greater in M H F than in N C with the various criteria used in evaluating the results If the data are reliable enough in revealing a definite and constant individual difference, it follows that the definite and constant difference between standing and recumbency must be quite real

Lundsgaard and Moeller,¹⁰ in considering the extrarenal factors influencing the elimination of phenolsulphonphthalein, are led to believe that the excretion of this dye depends on the local circulation in the kidneys, which may be influenced by conditions affecting the general circulation, and that consequently the phenolsulphonphthalein test is "of considerable value as an early and frequently occurring sign of circulatory insufficiency" White and his co-workers⁸ discuss at length the probable causes of the postural effects on renal activity The kidney vessels, perhaps, participate in the general body relaxation accompanying rest in bed Regardless of the mechanism of urine formation the caliber of the local blood vessels must be an important factor With a large capillary bed, other things being equal, there will be a greater filtration and a greater local circulation rate, although the two need not be coexistent, as indicated by the fact that water, pre-eminently dependent on filtration for its formation, may be increased while dye excretion is low, or decreased, with a high rate of excretion of dye That the local circulation rate is increased in recumbency is made the more probable by the fact that the general circulation rate is greater in recumbency, as shown by Field and Bock,¹² Rosen and White,¹³ Turner¹⁴ and others Abundant experimental data have accumulated to support the view that

¹² Field and Bock J Clin Investigation **2** 67, 1925

¹³ Rosen and White Am J Physiol **78** 158, 1926

¹⁴ Turner Am J Physiol **80** 601, 1927

the local blood supply to the kidneys is strongly controlled by nervous influences. If the influence of recumbency depends on the state of relaxation of the local blood supply, then it must in large measure depend also on nervous influences. That this might be so is indicated by the fact that, whereas, in changing from recumbent to standing the difference in elimination due to posture is clear, in changing from standing to recumbent, it is less clear. This fact may be interpreted to mean that in the early morning hours, coming from home to the laboratory, the body is still in low nervous tension from the previous night's rest. Hence, when the recumbent posture is assumed first, relaxation is easier. When, however, the recumbent posture is assumed after two hours' standing, relaxation is not so easily obtained. From table 2 it is easy to see that the difference in dye excretion attributable to posture is greater in changing from recumbent to standing than in making the reverse change. Furthermore, in M H F no difference could be attributed to the posture in changing from standing to recumbent. This subject was of a high strung nervous constitution, and his power of voluntary relaxation was not good, as shown during metabolism tests done on him in connection with some other work, and also by his difficulty of voiding small volumes of urine.

It will be interesting to determine to what extent posture influences renal activity in those with cardiorenal disorders. Will posture influence kidney function more in predominantly cardiac disorders than in predominantly renal conditions? Might the posture effect on the excretion of dye and water considered separately give a clue for differential diagnosis? It is hoped that these problems will be worked out by experimenters who can command proper facilities for further investigation.

As a result of the foregoing studies and the possibilities mentioned, it seems essential that renal function tests should be made with the patients in recumbent posture to eliminate one more variable, especially in borderline cases. It might be advisable, furthermore, to give water in fractional doses, with a view to assuring at the time of collection of the sample, a volume large enough to stimulate micturition even in nervous subjects, and yet small enough to exclude the possibility of renal inhibition by bladder distention.

SUMMARY AND CONCLUSIONS

1 The elimination of phenolsulphonphthalein in normal persons is greater in the recumbent posture than during standing. The difference (from 10 to 13 per cent) though definite is not marked, but should be taken into account in making phenolsulphonphthalein tests in borderline cases. The possibility that the difference might be greater in cardiorenal disorders is pointed out.

2 The effect of recumbency in increasing the volume of output is marked (from 50 to 200 per cent), confirming the results of the earlier investigators

3 The probable causes of these postural effects are discussed

4 On the basis of fifty-seven experiments on two subjects, at intervals of at least five days, it is shown that the hypodermic route is not as unreliable as is generally believed when the two hour eliminations are taken into account

5 The absence of toxic effects during the eight months covered in these studies is offered as one more evidence of the harmlessness of phenolsulphonphthalein. There is no evidence of the development of any increased storage or increased destruction in the body during this frequent and long continued use

6 Slight modifications in the technic of renal function tests are suggested

Book Reviews

CLINICAL PHYSIOLOGY IN RELATION TO MODERN DIAGNOSIS AND TREATMENT
By ROBERT JOHN STEWART McDOWELL, D Sc, M B, CRCP (EDIN),
Professor of Physiology, King's College, University of London Price, \$7
Pp 383, including an index, and a bibliography of six pages of recent
books and monographs New York D Appleton & Company, 1927

According to the author, the book is intended for senior medical students and practitioners of medicine whose busy lives do not permit them to read more extensive textbooks. The author, thus, assumes on the part of the readers the knowledge secured in a thorough course in the fundamentals of physiology, and on the basis of this he endeavors to analyze or explain symptoms of disordered functions in patients.

This is not the first nor the ablest venture in this field. The informed reader finishes the book with the feeling that Professor McDowell has not materially improved on Hewlett's "Pathological Physiology," and in many chapters he is clearly inferior to the latter. On the whole the Professor McDowell shows less critical judgment in the handling of conflicting data than the late Professor Hewlett.

In speaking of medical students, the author says that "it is extremely difficult, indeed almost impossible from the study of ordinary textbook physiology, for him to see why a cardinal symptom of cardiac disease should be breathlessness." One may assume that today the student in every up-to-date medical school is given more than textbook physiology. A senior medical student who is nonplussed by seeing dyspnea in a patient with marked cardiac impairment either does not know his physiology or he has not learned to think.

The chapters on "Psycho-therapeutics" and on "Balance of the Endocrine Organs" seem particularly weak and speculative. We have a puff for a much advertised book selling scheme in the following sentence: "A system of memory training such as Pelmanism, is efficacious in that it forms associations of value around certain words." One is assured that "psychology is a true science." It would be nearer the truth to say that the best psychologists are working earnestly to make psychology a science. The chapter on "Endocrine Balance" is filled with vague statements such as the following: "The pituitary body (anterior lobe) is specially related to the structural adaptation of the body to its physical environment." "The posterior lobe of the pituitary is concerned with the adaptation of the body processes necessary in the continuation of the species." The following appears as bald statements of proven facts: "Both these glands (thyroid, pituitary) become atrophied in contraction." "The thyroid and pituitary are normally antagonistic to the pancreas." "The sympathetic is associated with activity or metabolism, and the parasympathetic with anabolism." The author speaks of "the clinical phenomenon of growth," referring not to cancer, hyperplasia or wound healing, but to normal growth processes. He says that in pernicious anemia with a red cell count of 600,000 the general condition of the patient, provided he is resting, is quite good."

The up-to-date medical practitioner and the senior medical student in any first class school will reap meager profit in reading this volume. Even simple and well established facts are often obscured by the author's befuddled diction or attempts at philosophic abstraction. For example "Breathing is the movement made by the body to maintain pulmonary ventilation. As such it may be considered the external expression of the body for the need of oxygen." Platitudes like the following, are not rare: "A child whose diet is deficient cannot be expected to grow and the general ignorance in such matters is truly appalling."

As stated in the preface, the author starts for an ambitious albeit difficult goal, but at no point reaches the advanced posts already attained by the best books in normal and pathologic physiology

DAS VERSAGEN DES KREISLAUTES DYNAMISCHE UND ENERGETISCHE URSACHEN
VON PROF. DR. HANS EPPINGER, Direktor der Medizinischen Universitäts-
klinik in Freiburg, I, Br. DR. FRANZ KISCH and DR. HEINRICH SCHWARZ
Price, R. M. 16 50 Pp 238, with 56 illustrations Berlin Julius Springer,
1927

This monograph is an excellent attempt to analyze and explain the deficient physiology of patients with cardiac lesions (valvular and myocardic) in the light of recent physiologic researches on circulation, on blood, and on muscle physiology, notably those of Henderson, Hill, Meyerhof, Barcroft and others. The monograph contains, in addition, a good deal of experimental work on patients by the authors themselves. Most of these experiments deal with the oxygen required in rest and under measured work by patients with cardiac deficiency as compared to normal human beings. The report in the majority of such patients is higher oxygen requirement during rest and a much higher oxygen requirement during work as compared to normal men. The authors endeavor to explain this deficiency by an upset in the lactic acid metabolism in the body muscles due to more or less chronic asphyxia.

The monograph deals with the following main topics in the six chapters: The velocity of the blood flow as a measure of the peripheral circulation, the influence of physical work on circulation and on metabolism in patients with cardiac disease, the influence of physical work on lactic acid metabolism in cardiac deficiency patients, the significance of buffer processes for the circulation, experimental carbon dioxide poisoning, and, lastly, the theory of cardiac deficiency. The authors reach the conclusion that patients with cardiac deficiency produced more lactic acid than normal persons, and that there is developed in the former a deficiency in reconversion of lactic acid back to glycogen. In consequence of this there is an upset of blood neutrality in the direction of acidosis which in turn gradually causes impairment of the cardiac motor tissue.

The monograph reveals much thought and much able and conscientious experimentation. The conclusions are generally tentative and conservative. Only two criticisms may be directed against the volume, namely, many of the patients with cardiac deficiency recorded in the monograph probably had other pathologic processes besides the cardiac condition, so that before final conclusions can be reached similar experiments must be done on animals where one can be sure that the initial lesion at least is only that of the heart. There is also some carelessness in presenting the graphic data on many of the charts. Thus, for example, the date and the name of the patient is given without naming the particular disease. This is confusing as the reader must refer to various pages of the book to find the particular ailment from which the patient suffered. The authors also did not seem to be familiar with the fact that thyrotoxic patients require a high oxygen intake on doing physical work as compared to normal man. This fact was definitely established a number of years ago. But, as a whole the monograph is a distinct contribution to an interesting and difficult field of internal medicine.

SCIENTIFIC REPORTS OF THE GOVERNMENT INSTITUTE FOR INFECTIOUS DISEASES,
vol 5 The Imperial University Tokyo Shirokane-Damachi, Shibaku, 1926

The director of the Institute, Nagayo, although this volume contains none of his own contributions, has good reason to be proud of the work of his associates. The 650 pages are replete with interesting reports of experimental work which comes up to a high standard.

The section on biology contains a series of studies by Miyagawa (the editor of the volume and his assistants) on the effect of injections of autolysates

of various organs. Injections of such materials invariably cause profound degenerative changes in the corresponding organ. An adequate explanation is not vouchsafed for this unusual phenomenon.

The most striking feature of the volume, however, is the article by W. Nakahara on the filtrable virus of the Rous chicken sarcoma. By a well planned series of investigations, he has shown beyond a doubt that the so-called "causative agent" actually does contain live sarcoma cells. By staining methods he first showed that this "causative agent" still contained apparently viable sarcoma cells after drying, glycerination and passage through the Berkefeld filter. This fact is proved beyond a doubt by methods of tissue culture, so that the question can be considered as positively settled.

MODERN PRACTICE OF PEDIATRICS. By WILLIAM PALMER LUCAS. Price, \$8.50
Pp 962. New York: The Macmillan Company, 1927.

In this small volume of about 900 pages Dr. Lucas, with characteristic, unconventional scholarliness and scientific vigor, has brought the subject of pediatrics up to the immediate present. So true is this that even the well informed pediatrician, as well as the general practitioner and the advanced student, will find in it a constant source of reference for nearly all that is new in pediatrics. Especially valuable are the introductory chapters with their modern prophylactic note and the chapters on the blood and the diseases of the blood, on which the author speaks with well recognized authority. What the book lacks from the fact that no one man can any longer speak with final authority on all subjects pertaining to pediatrics is largely compensated by the vigorous and unconventional individuality of the author's presentation. In spite of the smallness of the book which carries with it the inevitable result that some subjects are treated too briefly to be of optimum service to the practitioner and the student, it can be warmly commended as a most valuable exposition of the modern Practice of Pediatrics.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR
VOLUME II. ADMINISTRATION AMERICAN EXPEDITIONARY FORCE. Price, \$3.40
Pp 1123. Washington, D. C.: Government Printing Office, 1927.

This volume, like its predecessors, is prepared with the greatest attention to detail. It is well indexed so that any particular topic can be easily found.

The first twenty chapters are devoted to the organization of the various subdepartments in the Surgeon General's Office, the next few chapters to various types of hospitals and the two chapters following on evacuation of patients to the United States. The final section is on medical departmental activities of the American Forces in France.

The volume is profusely illustrated with carefully prepared charts, maps and other figures.

THE SPECIFIC TREATMENT OF LOBAR PNEUMONIA

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Lobar pneumonia now ranks with tuberculosis in respect to mortality rate. In the registration area of the United States, the annual toll of deaths for each of these infectious diseases is approximately 100,000. While in both instances this figure is considerably lower than it was twenty years ago, it is still high enough to make them by far the most deadly of the infectious diseases. It is interesting that both of these diseases should be largely pulmonary. This fact suggests that there may be something in the anatomic structure of the lung which renders pulmonary infection difficult to control. Pneumonia is an acute disease and tuberculosis a chronic one, but in neither case has specific therapy met with much success.

Attempts to work out a successful serum treatment in pneumonia date from the discovery that lobar pneumonia was a pneumococcal infection, but not until recently have any encouraging results been obtained. Undoubtedly, the development of a satisfactory specific therapy in pneumonia has been greatly retarded by insufficient knowledge of the biologic characteristics of the pneumococcus. It was only seventeen years ago that Neufeld and Handel¹ discovered that there was a definite difference between various pneumococci in their reactions to immune serum, in other words, that pneumococci could be grouped into various serologic types. The serum produced with organisms of one type did not protect against infection with other strains. In view of this specificity of types these authors emphasized the importance of determining the type of pneumococcus in any individual case so that a corresponding immune serum might be used. They produced a potent antipneumococcus serum by immunizing horses with virulent pneumococci, and used it in the treatment of pneumonic patients by intravenous injections. Their results were encouraging. They called attention to the fact, since corroborated by others, that moderate amounts of serum had no beneficial effect and, for that reason, that large doses were indicated.

* The twelfth Mellon Lecture read before the Society of Biological Research of the University of Pittsburgh, May 12, 1927.

1 Neufeld and Handel. *Arch. d. k. Gsundtsamte* 34: 293, 1910.

The immunology of the pneumococcus was further cleared up by the work of Dochez and Gillespie,² and Dochez and Avery³ in their studies on types of pneumococcus. These investigators studied the various types of pneumococcus in the United States, and found that there were three dominant biologic groups, each possessing specific and characteristic immune reactions. In their experience, these three types comprised about 80 per cent of all strains of pneumococcus encountered in patients with lobar pneumonia, and represented apparently fixed types of a highly parasitic nature. These three types were referred to as types I, II and III. The remaining 20 per cent of their patients had pneumococci which were, for the most part, unrelated biologically, and which, for convenience, they classified collectively as pneumococcus type IV. This is really an assembly of all other types of pneumococcus, many of them just as distinct as types I, II and III. At first, it was thought that each individual strain of pneumococcus type IV was immunologically distinct, but Olmstead⁴ has shown that certain strains have many common characteristics, thus proving that there are definite subgroups in the type IV group of pneumococci. The type IV group is sometimes referred to as the "waste basket group" because it contains all pneumococci not contained in the three fixed types. Pneumococci of the type IV group are the organisms most frequently encountered in the secretions from the mouth of healthy persons. Dochez and his co-workers determined the incidence and death rate for the four so-called types of pneumococcus, and the more recent studies of Avery,⁵ Stillman,⁶ and others have thrown considerable light on the epidemiology of the disease with respect to the various types.

The discovery of the biologic types of pneumococcus made it clear why previous efforts to produce an effective serum against pneumonia had been unsuccessful. At the same time, these discoveries made it evident that the problem of producing a specific cure for pneumonia was destined to be much more difficult than it had been, for example, in the case of diphtheria and tetanus, in which the organism produced a highly specific toxin readily neutralized by antitoxin. It was now necessary to look on pneumonia as a group of biologically different infections, each of which required its own specific serum. However, the promising results obtained by Neufeld and Handel encouraged Cole and his associates at the Rockefeller Hospital to take up an extensive therapeutic investigation of the whole subject. A specific serum was produced in horses for both

2 Dochez, A. R., and Gillespie, L. J. A Biologic Classification of Pneumococci by Means of Immunity Reactions, *J. A. M. A.* **61** 727 (Sept. 6) 1913.

3 Dochez, A. R., and Avery, O. T. *J. Exper. Med.* **21** 114, 1915.

4 Olmstead, M. *J. Immunol.* **2** 425, 1917.

5 Dochez, A. R., and Avery, O. T. *J. Exper. Med.* **22** 105, 1915.

6 Stillman, E. G. *J. Exper. Med.* **24** 651, 1916.

type I and type II pneumococcus, and patients with pneumonia of these types were treated with the homologous serum. The studies of Cole and his co-workers⁷ mark the beginning of the modern specific therapy of pneumonia. Since the work of Cole, other investigators have taken up the problem, and much additional light has been thrown on the whole subject. I shall review briefly the work of these various investigators. Before taking up specific therapy proper, however, it might be well to recall a few facts pertaining to immunity to the pneumococcus, for it is only by an understanding of this question that one can appreciate the goal toward which immunologists are now working in the study of pneumonia.

IMMUNITY TO THE PNEUMOCOCCUS

It is not unusual for one person to have repeated attacks of pneumonia. For this reason, the idea has become prevalent that pneumococcal infection does not confer immunity. This, however, is not the case. Recurrent attacks of pneumonia in the same person are nearly always due to different strains of the pneumococcus, each producing, of course, its own specific immunity, but not conferring immunity against the other strains. Cecil and Blake⁸ found that monkeys recently convalescent from an attack of pneumococcus type I pneumonia could not be reinfected with pneumococcus type I. They could be infected, however, with pneumococcus types II, III or IV. This specific immunity was also demonstrable after pneumonia caused by the other types. Dochez, Blake and, more recently, Baldwin and Rhoades, have pointed out that patients recovering from lobar pneumonia develop immune bodies against the pneumococcus at about the time of the crisis. The inference is that these antibodies play a significant part in immunity to the pneumococcus.

It is a comparatively easy matter to immunize animals against the pneumococcus. This immunity can be conferred by either active or passive immunization. As far back as 1910, Neufeld and Handel⁹ showed that animals vaccinated with killed or living cultures of pneumococcus, developed an immunity against the organism. This fact has been amply verified by other investigators, more recently by Cecil and Steffen¹⁰ who found that monkeys vaccinated against the pneumococcus were immune to pneumonia caused by a pneumococcus of the same type.

Chart 1 shows the variations in temperature and the number of white blood cells in type I by three subcutaneous injections of pneumococcus type I vaccine. Monkeys 13, 14 and 15 received the vaccine, monkey 21

7 Cole, R. Treatment of Pneumonia by Means of Specific Serums, *J. A. M. A.* **61** 663 (Aug. 30) 1913.

8 Cecil, R. L., and Blake, J. A. *J. Exper. Med.* **31** 685, 1920.

9 Neufeld and Handel. *Arb. a. d. k. Gsundheitsamte* **34** 293, 1910.

10 Cecil, R. L., and Steffen, G. I. *J. Exper. Med.* **34** 245, 1921, **38** 149, 1923.

was an unvaccinated control Three weeks after the completion of vaccination, an attempt was made to infect these monkeys by injecting them intratracheally with a living virulent culture of pneumococcus type I The three vaccinated monkeys remained well, the control developed pneumococcus type I pneumonia associated with pneumococcus type I septicemia

In 1917, Cecil and Austin¹¹ vaccinated 12,519 recruits against pneumonia at Camp Upton, using a mixed vaccine composed of equal parts of pneumococcus types I, II and III These men were under observation

Monkey 13

120 bld killed Pn I subcutaneous

Monkey 14

120 bld killed Pn I subcutaneous

Monkey 15

120 bld killed Pn I subcutaneous

Monkey 21

Control

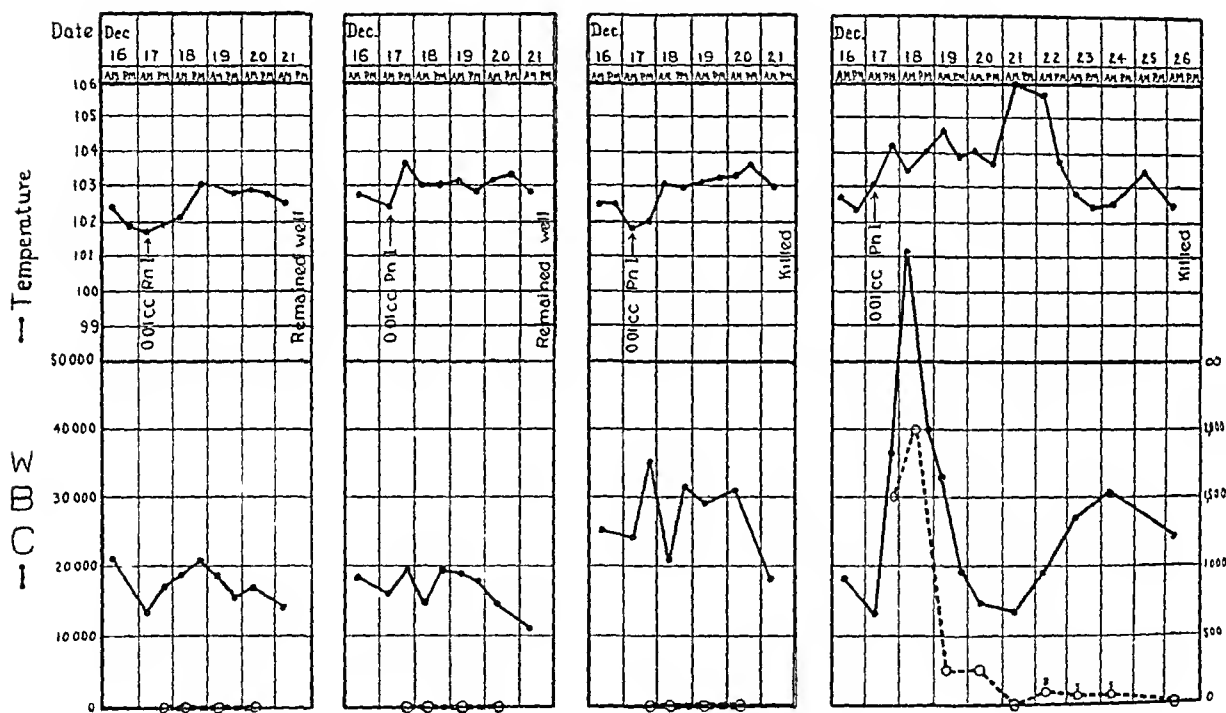


Chart 1—Active immunization of monkeys against pneumococcus type I pneumonia following vaccination with pneumococcus type I vaccine

for nearly three months subsequent to vaccination During that time, only one case of pneumonia of the fixed type occurred among the vaccinated troops, and this patient had received only one inoculation of vaccine Among the 19,481 unvaccinated troops, there were twenty-six cases of pneumonia of the fixed type during the same period of time Furthermore, there was considerably less type IV pneumonia among the vaccinated troops than among the unvaccinated

Active immunization, therefore, against the pneumococcus is feasible It is also possible to confer a passive immunity on animals against

11 Cecil, R L, and Austin, J H J Exper Med 28 19, 1918

pneumococcus infection, and this, of course, has considerable significance from the standpoint of serum therapy. If the serum from an animal immunized against pneumococcus type I is injected into a mouse, the mouse is immediately protected against pneumococcus type I infection.

The same is true of monkeys. In chart 2 are shown the variations in temperature and the number of white blood cells of three monkeys that

Monkey 300

Monkey 301

Monkey 302

Monkey 303
Control

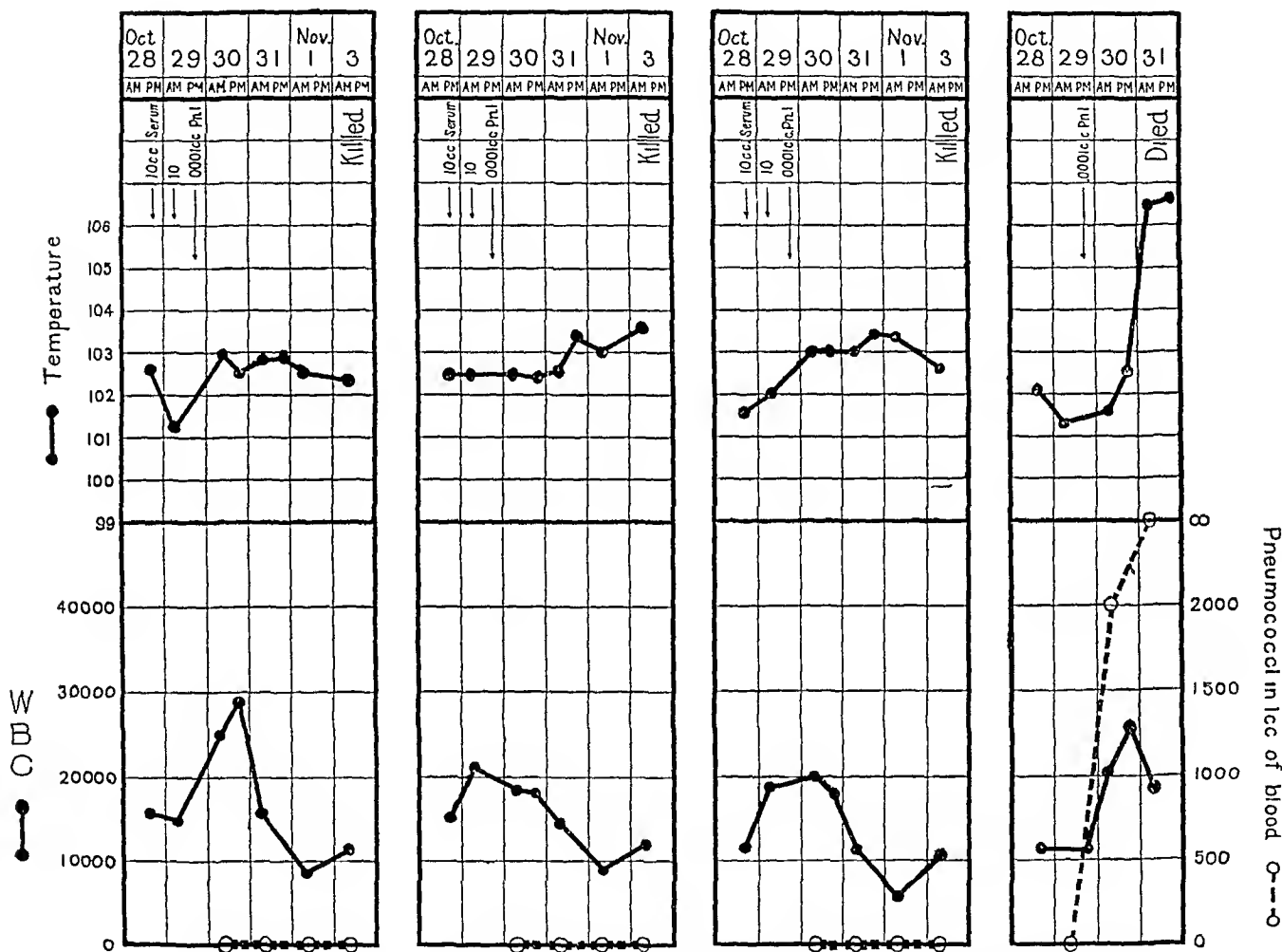


Chart 2—Passive immunization of monkeys against pneumococcus type I with type I serum

were passively immunized against pneumococcus type I. Monkeys 300, 301 and 302 each received two intravenous injections of type I anti-pneumococcus serum. Twenty-four hours later, an attempt was made to infect these monkeys by intratracheal injection of a living virulent culture of pneumococcus type I. All three monkeys remained well. The control monkey, number 303, had not received any serum and the intratracheal injection of a virulent culture of pneumococci produced a fulminating pneumonia, septicemia and death.

Immunity to the pneumococcus is probably dependent on a number of factors. The humoral factors that are known are agglutinins, precipitins, opsonins and the so-called protective bodies. The protective bodies receive their name from the fact that when mice are injected with virulent cultures of pneumococci, they are protected from death by the simultaneous injection of a certain amount of antipneumococcus serum. None of these immune bodies has been isolated in a chemically pure form, but they can all be removed from serum by various chemical procedures which will be discussed later.

The protective bodies, like the other immune bodies, are highly specific for type, and are usually demonstrable in the serum of patients recovering from pneumonia at about the time of the crisis. Sometimes,

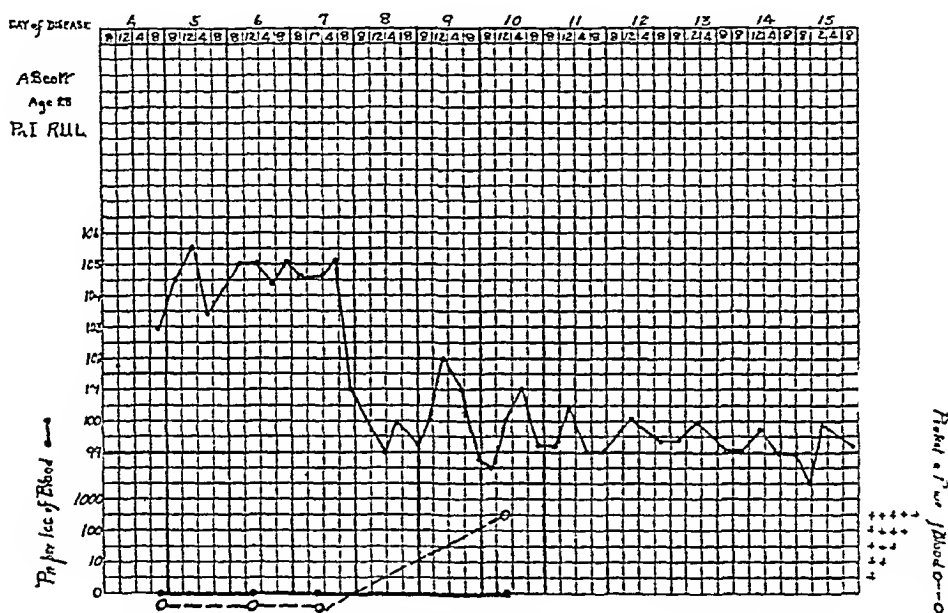


Chart 3—Development of protective substance in the blood of a patient with pneumococcus type I pneumonia after the crisis

however, they are present several days before the crisis. Chart 3 shows the development in a patient with type I pneumonia of a protective substance in the circulating blood after the crisis. The patient had his crisis on the morning of the eighth day. Up to this time, no protective substance had been present in the circulating blood. On the tenth day, the blood was again tested on mice, and enough protective substance was present to protect mice against 10 000 fatal doses of a culture of pneumococcus type I.

In addition to the humoral factors in immunity to the pneumococcus, there are important cellular factors. The leukocytes notably the polymorphonuclear type, play an important rôle in pneumococcus immunity, and there is considerable evidence to show that the epithelial cells lining the terminal alveoli in the lung are vitally concerned.

One of the most interesting of recent developments in the field of immunity to the pneumococcus has to do with the so-called soluble substance. Physicians are chiefly indebted for their knowledge of this interesting product to Avery and his co-workers. The soluble substance, or S substance as it is frequently called, is a polysaccharid which is always present in solution in broth filtrates of virulent cultures of pneumococcus. It can also be demonstrated in empyema fluids of pneumococcal origin and in the blood of patients with pneumococcus septicemia. It is usually present in the urine of patients with severe pneumonia. The soluble substance, like the protective substance, is rigidly specific for each type of pneumococcus. It is nontoxic and nonantigenic, but it has the important faculty of neutralizing the immune bodies produced by the patient. The soluble substance originates in the capsule of the pneumococcus and appears to enhance the virulence of the organism chiefly by preventing its phagocytosis by the leukocytes.

There has been considerable discussion recently as to whether the pneumococcus is capable of producing a toxin. Certainly, the pneumococcus has not been shown to produce a soluble toxin in the commonly acknowledged sense. Cole¹² showed that when solutions of pneumococci, obtained by dissolving them in bile salts, were injected intravenously into guinea-pigs, they produced sudden death similar to that seen in acute anaphylaxis. Cole admitted, however, that there was considerable doubt whether the substance producing this effect was identical with or related to the substance giving rise to the lesions and symptoms associated with pneumococcus infection. Solutions containing dissolved pneumococci have been found to be hemolytic, and there is evidence that this hemolytic substance exists pre-formed in the bacterial cells.

Recently, Clowes, Jamieson and Olson¹³ claimed to have demonstrated a toxic substance in the filtrates of cultures of pneumococcus. This toxin does not often kill laboratory animals, but when injected subcutaneously or intravenously, it is capable of producing hemorrhagic lesions in the lungs. Olson¹⁴ claimed that the serum of animals, immunized against this so-called toxin, contains an antitoxin which when mixed with toxin will prevent the development of the hemorrhagic lesions in the lungs. This toxin also gives a positive reaction to skin test in rabbits, which can be neutralized by the antitoxin. These investigators said that the pneumococcus toxin and antitoxin which they prepared apparently are not specific for type. On the basis of this work, Clowes, Jamieson and Olson have prepared "antitoxin" for therapeutic purposes, but, so far, this product has not received any extensive

12 Cole, R. J. *Exper. Med.* **20** 346, 1914

13 Clowes, G. H. A., Jamieson, W. A., and Olson, J. G. *Proc. Soc. Exper. Biol. & Med.* **23** 334, 1925-1926

14 Olson, J. G. *Proc. Soc. Exper. Biol. & Med.* **23** 331, 1925-1926

clinical test My co-workers and I have treated a few patients at Bellevue Hospital with this antitoxin but the results have not been impressive

CAUSE OF DEATH IN PNEUMONIA

Before proceeding to an actual discussion of the specific treatment of patients with pneumonia I shall discuss briefly the cause of death in this disease In city hospitals, about 30 per cent of all patients with lobar pneumonia die There are slight variations in this figure for different hospitals and different localities, but any large group of carefully selected cases of lobar pneumonia will show a death rate close to this figure It is easy to understand why a considerable number of these patients die, they are old or they are suffering from some chronic systemic disease which has already undermined their resistance to infection But the question which interests one particularly is Why is pneumococcus infection fatal in a certain percentage of healthy young adults?

TABLE 1—*Death Rate in Pneumonia for the Various Types*

| | Cases | Died | Per Cent |
|----------|-------|------|----------|
| Type I | 352 | 73 | 20.7 |
| Type II | 221 | 93 | 42.0 |
| Type III | 161 | 67 | 41.6 |
| Type IV | 373 | 109 | 29.2 |
| Total | 1,107 | 342 | 30.8 |

The death rate of pneumonia varies considerably with the type In 2,000 cases of typed pneumococcus pneumonia recently analyzed by Cecil, Baldwin and Larsen¹⁵ the death rate for patients that received no specific therapy is shown in table 1

It will be seen from these figures that while types II and III pneumonia are the severest forms, types I and IV actually kill more patients because they are so much commoner than the other two types Type I pneumonia has the lowest death rate of all the four types presumably because it is essentially the pneumonia of young people

For many years physicians have assumed that patients with pneumonia die of heart failure but if this is true it is not heart failure in the ordinary sense There is considerable evidence to show that in many instances the patient with pneumonia dies of vasomotor paralysis In fatal cases the blood pressure is usually extremely low for several

¹⁵ Cecil, R. L. Baldwin, H. S. and Larsen, N. P. Lobar Pneumonia. A Clinical and Bacteriologic Study of Two Thousand Typed Cases, Arch. Int. Med. 40:253 (Sept.) 1927

hours or even days before death occurs. But one may go back a step further and ask the reason for the heart failure or the vasomotor paralysis.

There is one fact the significance of which all students of pneumonia are agreed on, namely, that fatal pneumonia is usually a septic pneumonia. Patients dying with pneumococcus pneumonia nearly always show a considerable number of pneumococci in the circulating blood. In this respect, pneumonia is like most other pyogenic infections. Starting out as a local process in the lung, it soon produces symptoms of toxemia, but the life of the patient is rarely in danger as long as the blood stream remains sterile. With the development of septicemia, the situation becomes much more serious. In Cole's studies, 343 cases of lobar pneumonia in which blood cultures were negative showed a death rate of only 11.6 per cent, while in 119 cases in which the blood cultures were positive, the death rate was 67.1 per cent. Moreover, the death

TABLE 2—*Blood Cultures in Case of Lobar Pneumonia of Various Types*

| Type of Pneumococcus | Cases Studied | Cases Showing Positive Blood Cultures | | Cases Showing Sterile Blood Cultures | |
|-------------------------|------------------|--|-------------|---|----------|
| | | Cases | Deaths | Cases | Deaths |
| I | 39 | 11 | 6 | 28 | 3 |
| II | 22 | 14 | 13 | 8 | 1 |
| III | 11 | 4 | 3 | 7 | 1 |
| IV | 35 | 8 | 7 | 27 | 2 |
| Total | 107 | 37 | 29 78.3% | 70 | 7 10% |

rate was directly proportional to the number of pneumococci present in the blood. In patients who showed over twenty colonies per cubic centimeter of blood, the death rate varied from 80 to 100 per cent. Similar observations were obtained in our studies of pneumococcus septicemia at Bellevue Hospital. In 107 cases of lobar pneumonia of various types, frequent blood cultures were taken throughout the course of the disease.

In table 2 the relation of bacteremia to the death rate is clearly shown. In seventy cases with sterile blood culture, the death rate was only 10 per cent, whereas, in thirty-seven cases with positive blood cultures the death rate was 78.3 per cent. Therefore, while one is hardly in a position to say that death in pneumonia is actually due to pneumococcus septicemia, one can at least say that death in pneumonia is associated in a high percentage of cases with pneumococcus septicemia and that pneumococcus septicemia is usually followed by death. In studying experimental pneumococcus pneumonia in several hundred monkeys, I have seen a great many of these animals die of the disease, but not a single case that I can recall in which death was not accompanied by a large number of pneumococci in the blood.

SIGNIFICANCE OF IMMUNE BODIES IN PNEUMOCOCCUS
PNEUMONIA

I have already referred to the fact that recovery in pneumonia is accompanied by the development of various immune bodies in the blood of the patient. Agglutinins, precipitins, complement-fixing bodies and protective bodies make their appearance at about the time of the crisis and persist in the blood of the convalescent patient for several weeks or even months after recovery. So regularly does this occur that physicians have learned to be fearful about the outcome of the disease in

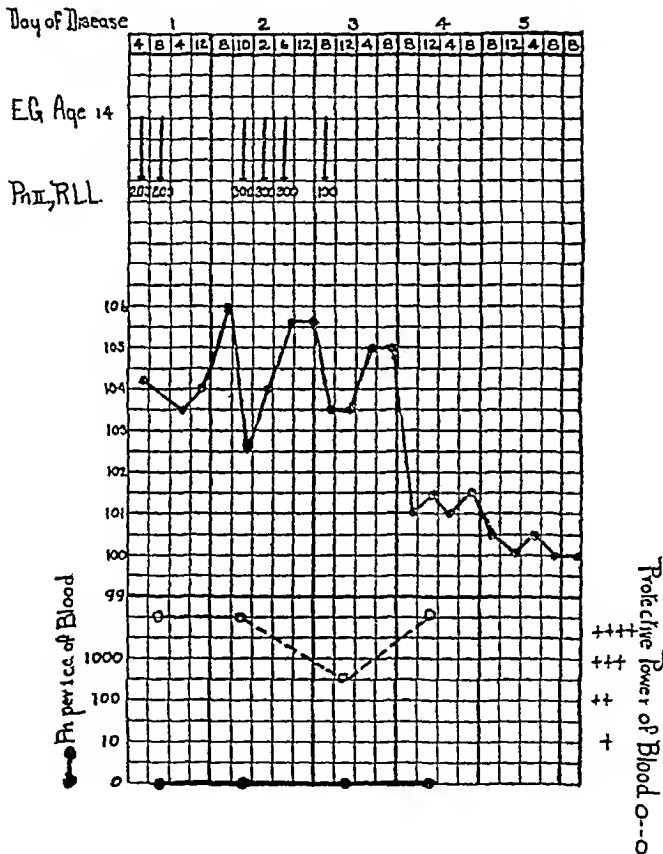


Chart 4—Variation in temperature of a patient with pneumococcus type II pneumonia. Immune bodies were in the blood on the first day of the disease.

any patient if the blood shows a complete absence of immune bodies, even when the temperature, pulse and respiration have returned to normal. Sometimes, the immune bodies appear in the blood two or three days before the crisis, this, of course, is a good omen. In one case of type II pneumonia which my co-workers and I studied in a boy, aged 15, a large amount of protective substance was found in the circulating blood on the first day of his disease. The infection ran a short course (chart 4), the temperature becoming normal on the fifth day. But there were two other significant factors in this case. The patient gave

little evidence of toxemia. He wanted to sit up in bed and read even when the temperature was 105 F, and there was never any delirium. The second significant factor was that pneumococci did not appear in the blood at any time. The latter point is particularly significant. In a series of twenty-five cases of pneumonia studied in our laboratory, in which blood was taken every day or two to determine the presence or absence of pneumococci and of protective bodies, bacteria and specific antibodies occurred simultaneously in the blood only once, and in that instance the blood showed only three or four pneumococci per cubic centimeter of blood. From this it may be inferred that one of the most important functions of immune bodies is to prevent the entrance of pneumococci into the general circulation. On the other hand, patients

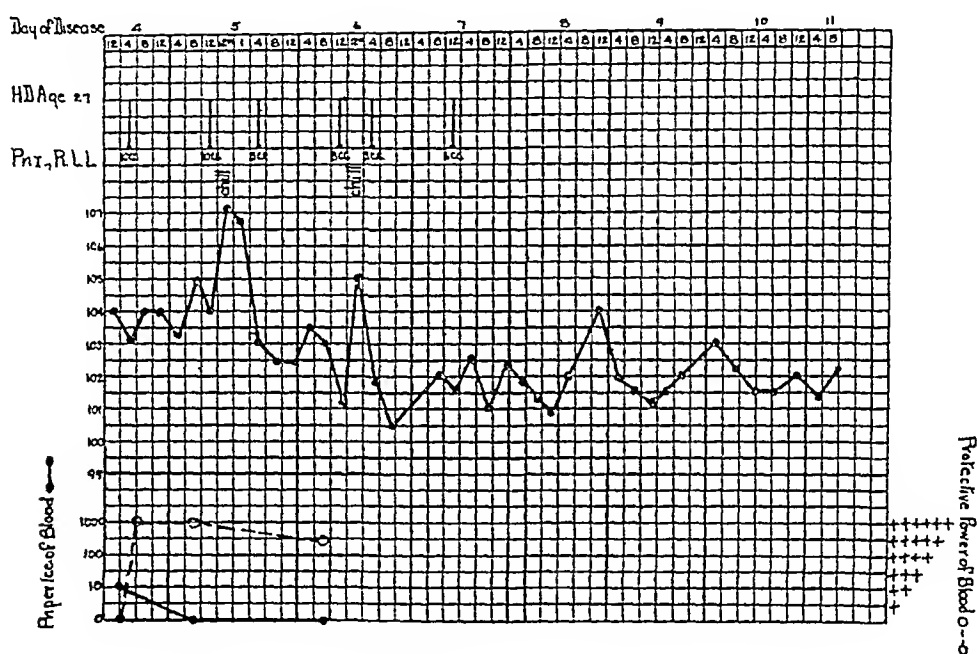


Chart 5—Variations in temperature of a patient with pneumococcus type I pneumonia with positive blood culture. Empyema developed in spite of immune bodies in patient's blood.

who die of pneumonia rarely show immune bodies in the circulating blood, but, as I have already shown, they usually do show a severe grade of pneumococcic sepsis. In some of these fatal cases, the blood contains so many pneumococci during the last hours of life that it is almost impossible to count the colonies on a plate. In the blood and urine of these septic patients a large amount of the soluble substance of Avery can be demonstrated. As this substance has the faculty of neutralizing the immune bodies, one may infer that whatever immune substance has been manufactured by the patients has been completely neutralized by the soluble substance produced by the pneumococci in the circulating blood. While the protective antibodies appear to shield the patient against pneumococcus sepsis, they do not necessarily prevent

certain other pneumococcus complications. For example, chart 5 shows the temperature curve of a patient with pneumococcus type I pneumonia in which the crisis was accompanied by the development of protective antibodies in the patient's blood. A few days later, this patient developed empyema. Examination of the blood showed that the patient's serum still contained a considerable amount of immune bodies in spite of the empyema. The significant point is that the blood remained sterile and the patient eventually recovered.

What is the exact function of the protective antibodies? The studies of Blake,¹⁶ and the more recent work of Robertson and Sia¹⁷ show that the pneumococcus immune bodies are necessary for the phagocytosis of virulent pneumococci, in this respect resembling Wright's opsonins. Indeed the protective antibody and opsonin may be identical substances. Virulent pneumococci will grow even in the most highly potent anti-pneumococcus serum but under such conditions the pneumococcus rapidly loses its virulence. Years ago, Neufeld and Handel showed that the leukocytes do not take up virulent pneumococci, while avirulent strains undergo rapid phagocytosis, when virulent pneumococci are mixed with normal human blood and allowed to stand in the incubator for twenty-four hours, the pneumococcus grows freely. In the blood of a patient convalescing from pneumonia, the pneumococcus usually fails to grow under the same circumstances. Furthermore, if immune serum is added to the blood of a normal man, the pneumococcus will not grow. However, if the blood of the convalescent patient is first centrifugalized and the leukocyte cream removed, the pneumococcus grows freely. From this evidence, it appears almost certain that the final destruction of pneumococci is accomplished by the leukocytes, but that they will not undertake this important function until the pneumococci have been prepared by the serum for phagocytosis.

Just as the protective bodies are conducive to phagocytosis, so the soluble substance interferes with phagocytosis by blocking the immune bodies and thereby allowing the pneumococci to maintain their full virulence.

In pneumococcus infection in man, the ultimate outcome depends on whether the pneumococci or the leukocytes gain supremacy. If the host produces enough immune bodies, the infection remains localized in the lung, and the patient recovers. On the other hand, if the pneumococci produce enough soluble substance to more than neutralize the immune bodies, phagocytosis is inhibited, the infection spreads, the pneumococci gain access to the blood stream and the patient eventually dies with pneumonia sepsis.

¹⁶ Blake, F. G. *J. Exper. Med.* **26** 563, 1917.

¹⁷ Robertson, O. H., and Sia, R. H. P. *J. Exper. Med.* **39** 219 (Feb) 1924. **40** 467 (Oct) 1924.

THERAPEUTIC INTRODUCTION OF PROTECTIVE SUBSTANCE
INTO THE BLOOD

In the fight then between the pneumococcus and the human host, septicemia spells death and immune bodies recovery for the patient. Herein lies the rationale of our efforts to produce a specific therapy for lobar pneumonia. The modern serum treatment of patients with pneumonia consists essentially in the artificial introduction of pneumococcus immune bodies with the hope of assisting the patient in his efforts to produce immunity against the disease.

The artificial immunity which one tries to establish in the pneumonic patient is probably antibacterial. By the introduction of an excess of protective antibodies one hopes to sensitize or opsonize the pneumococci and thus prepare them for phagocytosis by the leukocytes. So far as is known, there is no genuine antitoxic quality in any pneumococcus serum.

It should be emphasized here that the various specific therapeutic agents are essentially alike in their general nature in that they all contain protective antibodies and usually agglutinins and precipitins. Up to the present time, three of these specific therapeutic agents have been studied in our clinic and laboratory at Bellevue Hospital, (1) the type I and type II antipneumococcus serum of Cole, (2) Huntoon's pneumococcus antibody solution and (3) Felton's concentrated antipneumococcus serum.

TYPE I ANTIPNEUMOCOCCUS SERUM

It must be evident from what has already been said regarding the specificity of pneumococcus types that the efforts of early investigators to produce efficient antipneumococcus serum were frustrated by their failure to distinguish between these various groups of pneumococci.

Following the work of Neufeld and his co-workers, Rufus Cole took up the question of specific therapy at the Hospital of the Rockefeller Institute. Working first with pneumococcus type I, Cole's type I serum was prepared as follows:

Horses were immunized by injections first of dead and then of living cultures of type I pneumococci. The serum of the horse was tested for its power to produce agglutination of pneumococci of this type, and also for its effectiveness in protecting mice against multiple lethal doses of the same organism. Cole used the so-called "mouse protection test" to determine the therapeutic power of type I serum. The standard which he finally set for an accepted therapeutic serum was one in which the serum should be of such a strength that 0.2 cc. would protect mice regularly against at least 0.1 cc. of a pneumococcus type I culture of such virulence that 0.0000001 cc. of an eighteen hour broth culture would kill a mouse within forty-eight hours. When the horse had produced a serum of such potency, it was bled under aseptic conditions, and after the blood had clotted, the serum was removed and placed in bottles for use.

Cole advocates the use of type I serum for only those patients whose sputum or blood have been found to contain pneumococcus type I. This preliminary examination causes some loss of time, but Cole claims, and I think rightly, that patients with other types of pneumonia should not be subjected to type I serum.

In type I cases, the serum is administered as follows:

In order to avoid anaphylactic accidents, the patient is first questioned for a history of previous injections of horse serum and also for a history of hay-fever or asthma, as persons having such symptoms are likely to be sensitive to various proteins including those in serum. In any event, an intradermal skin test is performed with a small tuberculin syringe, 0.02 cc of diluted horse serum being injected into the skin. If the reaction to the test is negative, the wheal produced by the injection of serum fades away rapidly. If sensitiveness does exist, a genuine urticarial wheal begins to develop, usually within five minutes, which may increase slowly in size up to that of a half dollar. This lesion usually reaches its maximum within an hour and then fades away rapidly.

Cole believes that all patients who are to receive antipneumococcus serum should receive a "desensitizing" dose of serum six or eight hours before the first intravenous injection. The reason for this is that occasionally one sees a patient in whom the reaction to the skin test is negative and yet in whom, on the injection of large amounts of serum, symptoms of serum sensitiveness appear. It is therefore advisable to inject 1 cc of antipneumococcus serum subcutaneously even though the reaction to the skin test is negative.

In the small percentage of patients who are found to be sensitive to horse serum, a more thorough method for desensitization must be employed. This consists in giving small amounts of serum subcutaneously at half hour intervals, doubling the size of the dose at each injection. After 25 cc of serum have been given by this method, larger doses, consisting of from 50 to 100 cc may be injected intravenously without fear of shock.

Type I serum is administered intravenously. The serum is usually allowed to run into the vein by gravity and should be injected slowly. Cole advises that the injection of the first 10 to 15 cc of serum should occupy from ten to fifteen minutes. During this period, one watches carefully for any change in the patient's appearance and for increased rapidity of the pulse, dyspnea, cyanosis or urticaria. If these symptoms appear, it is well to stop the injection of serum for a few minutes to see if the symptoms increase in severity. Usually, they disappear rapidly and the treatment can be resumed. Experience has shown that if antipneumococcus serum is to be successful, it must be given in large doses. It is necessary to inject a sufficient amount of serum to produce a balance of protective antibodies in the patient's blood, such as that which occurs during natural recovery from the disease, for, as already indicated, it is largely on this factor that recovery depends. An effective concentration of immune bodies can be obtained in the blood only after all the circulating soluble substance has been neutralized. Once a permanent balance of antibodies in the blood has been achieved, a fall in temperature and a noticeable improvement in the condition of the patient should soon follow. The amount of serum necessary will vary in each case. Cole recommends an initial dose of from 90 to 100 cc. The frequency and size of the succeeding doses must be regulated largely by the effects obtained by those preceding, but in most cases the serum should be given every eight hours in doses of from 90 to 100 cc until the patient's temperature drops

to 100 F or less and remains at that point. The patient should be under observation day and night and the treatment should be given by night as well as by day whenever necessary.

REACTIONS TO SERUM

Cole describes three types of reaction which may follow the injection of antipneumococcus serum: (1) the true anaphylactic reaction, (2) the thermal reaction and (3) the serum disease.

In persons who are sensitive to horse serum a more or less severe asthmatic attack with dyspnea and flushing of the face may develop at once or within from fifteen to twenty minutes after the introduction of serum, followed by cyanosis, sweating, cough, anxiety and an urticarial rash. An anaphylactic reaction, unless extremely severe, is usually relieved by a hypodermic injection of from 0.5 cc to 1 cc of a 1:1,000 dilution of epinephrine. These reactions rarely occur, and if sensitive patients are properly desensitized, serious anaphylactic reactions will probably never occur.

Another type of reaction which may follow the intravenous injection of serum is the so-called thermal or foreign protein reaction. This comes on usually from thirty minutes to one hour after injection and is characterized by a chill, some cyanosis, rapid rise in temperature of from 1 to 3 degrees, which is followed by an equally rapid fall to normal or even to subnormal. During the fall there is usually profuse perspiration. After the reaction, the patient usually feels much improved. Sometimes the temperature remains normal, but usually it begins to rise again after a few hours. Cole does not believe that this reaction is of benefit to the patient and thinks it should be avoided if possible. Patients with this type of reaction need little treatment other than reassurance and the application of heat to the extremities.

Following the administration of horse serum, a group of symptoms frequently occurs which are referred to as serum sickness or serum disease. These symptoms usually make their appearance from seven to fourteen days following the administration of serum and consist of fever, skin rashes, most frequently urticaria or erythema, edema of the skin, general adenopathy and pain and swelling in the joints. The attack usually lasts from a few days to a week and may recur one or more times at intervals of a few days. Not all patients receiving serum show the symptoms. According to Cole, mild symptoms of serum disease appear in about one-half of the treated patients, severe attacks, rarely. The severe cases are more likely to occur in patients who receive large doses of serum.

RESULTS OF SERUM TREATMENT

The most striking effects of serum treatment in type I pneumonia are usually seen after a so-called thermal reaction. Sometimes the

clinical change after one of these shock reactions is spectacular, and the marked amelioration of symptoms presents the features of a natural crisis. In cases in which a thermal reaction does not occur, a change in the patient's condition is usually not so marked. Even when chill is absent, the patient's mental condition is generally improved, cyanosis becomes somewhat less, and the pulse rate falls. No doubt, in many cases this improvement is due to an actual sterilization of the blood. Cole thinks that, in addition to its other effects, antipneumococcus serum may have a detoxifying effect.

In our experience, the most striking results in type I therapy have been

1 When serum was administered on the first or second day of the disease and the whole infection was aborted, the temperature dropped rapidly to normal. In such cases, the physical signs never become frank, and the patient is practically well in forty-eight to seventy-two hours.

2 Type I serum produces a marked improvement in septic patients whose blood contains 50 or 100 colonies of pneumococcus type I per cubic centimeter by sterilizing the blood and thereby reducing the infection to a localized process. Cole believes that the administration of serum does not cause any change in the rate of resolution of the lung tissue already involved. When given early, however, there is no doubt that the serum prevents spread of the infection to healthy tissue. There is no evidence that serum diminishes the incidence of pneumococcal complications.

EFFECT OF SERUM ON MORTALITY RATE

In Cole's series of 195 patients with the pneumococcus type of pneumonia that were treated with serum, there was a mortality rate of only 9.2 per cent. In type I cases, before serum treatment was commenced, the death rate had been from 25 to 30 per cent. According to these figures, therefore, the death rate for patients with type I pneumonia had been reduced two-thirds by the use of serum.

Since the original report of Cole, the largest group of cases of type I pneumonia in which the patients have been treated with antipneumococcus serum is that of Wadsworth¹⁸ who, in 1924 reported the cases of 445 in New York state treated with a highly potent type I serum prepared by the New York State Department of Health. When the cases studied in army camps were eliminated, there were 277 cases with fifty deaths, a death rate of 18 per cent. In 344 patients with type I pneumonia that had not received serum the death rate was only 19 per cent, a figure only slightly higher than that for the treated patients.

18 Wadsworth, A. B. *Am J Hyg* 4 119 (March) 1924.

Shortly after Wadsworth's article was published, Locke¹⁹ reported a detailed study of 145 cases of type I pneumonia in which the patients were treated with serum, with a mortality rate of 17.2 per cent as compared with a mortality of 16.9 per cent in 70 untreated patients.

After reading the excellent studies of Wadsworth and of Locke, one wonders why the results reported in their series of cases were so much less promising than those obtained by Cole. Wadsworth's patients were treated with a potent serum but by many different physicians, some of whom probably did not administer serum in sufficiently large doses. Locke's patients received plenty of serum, but he does not give any record of its potency.

THE EFFECT OF TYPE I SERUM IN EXPERIMENTAL TYPE I PNEUMONIA

It is not surprising that, in view of the results obtained by Wadsworth and by Locke, the popularity of type I serum has decreased considerably since its original introduction by Cole, and yet the low death rate obtained by Cole (9 per cent) is significant, furthermore, the results obtained in the treatment of monkeys that had experimental type I pneumonia with type I serum are most convincing. Cecil and Blake found that type I antipneumococcus serum has a highly specific therapeutic action on monkeys with experimental pneumococcus type I pneumonia.

Chart 6 shows the variations in the temperature of two monkeys with experimental pneumococcus type I pneumonia. Twenty-four hours after injection with a lethal dose of a culture of pneumococcus type I, a course of small intravenous injections of type I serum was started in monkey 94. The first injection sterilized the blood, and the temperature was reduced to 102° F. after five injections. Treatment was then stopped, but the temperature rose again on the fifth day. Two more injections of serum given at different times produced a crisis, and the monkey remained well thereafter. The control, monkey 93, did not receive serum and ran a typical course with septicemia, dying on the twelfth day.

Chart 7 shows the effect of type I serum on monkeys with experimental type I pneumonia when serum treatment was started late in the disease. These charts are instructive in that they show that when treatment with serum is started late, the serum is still capable of sterilizing the blood, but that it exerts practically no influence on the temperature. The lives of both treated monkeys (99 and 113) were saved, while the control monkey (112), in this instance treated with normal horse serum, died on the sixth day of the disease with lobar pneumonia and pneumococcus septicemia. Chart 8 is in sharp contrast to the

¹⁹ Locke, E. A. Treatment of Type I Pneumococcus Lobar Pneumonia with Specific Serum, *J. A. M. A.* 80:1507 (May 26) 1923.

preceding experiment showing the striking effect of serum when administered in large doses early in the disease. Both monkeys were given lethal doses of pneumococcus type I culture, and both recovered promptly after receiving four doses of serum.

To my mind, the three experiments just presented prove the therapeutic value of type I serum more convincingly than any number of statistics.

MONKEY 94

TREATED WITH TYPE I ANTIPNEUMOCOCCUS SERUM

MONKEY 93

CONTROL

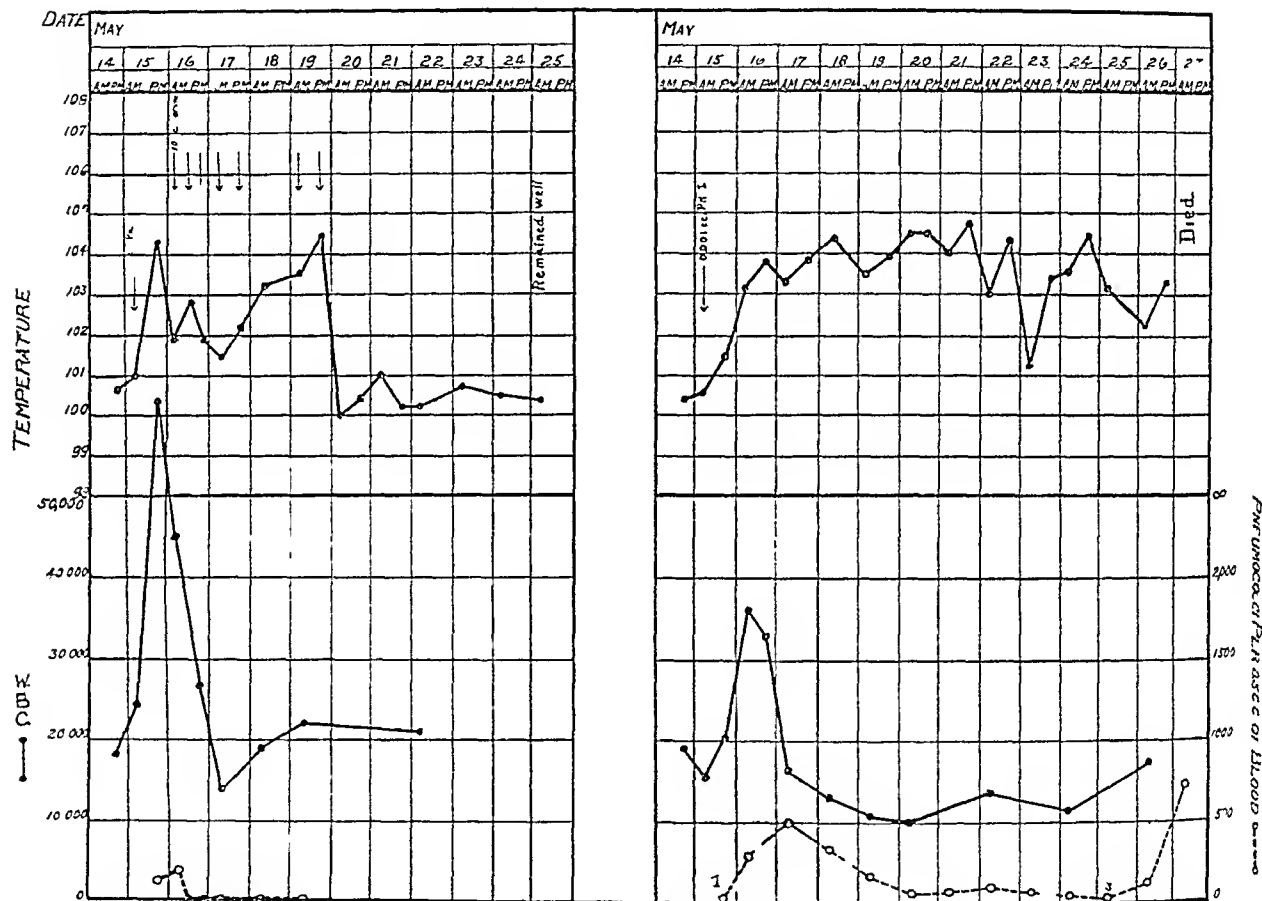


Chart 6—Treatment of monkey with pneumococcus type I pneumonia with type I antipneumococcus serum

Why has type I serum not come into more general use in the treatment of patients with type I pneumonia? Perhaps the most important obstacle to its use has been the difficulty in getting an early bacteriologic diagnosis. In many cases sputum is not obtainable until several days after the onset of the disease, and then too often at least twenty-four hours elapses before the laboratory makes its report. This means that treatment with serum is begun late in the disease when its therapeutic effect is not as striking as when it is administered early. Another objection to the gen-

eral use of type I serum is the fear of reactions, either anaphylactic or thermal. Another reason for its lack of popularity is the technical difficulty connected with the proper administration of large doses of serum. Cole advises that the serum be diluted with an equal amount of saline solution, and this means that three times in every twenty-four hours the busy practitioner must inject 200 cc of diluted serum intravenously. Finally, a most important obstacle to its further use is the fact that many observers have not been able to duplicate the low mortality figures obtained at the Rockefeller Hospital. The reasons for this failure

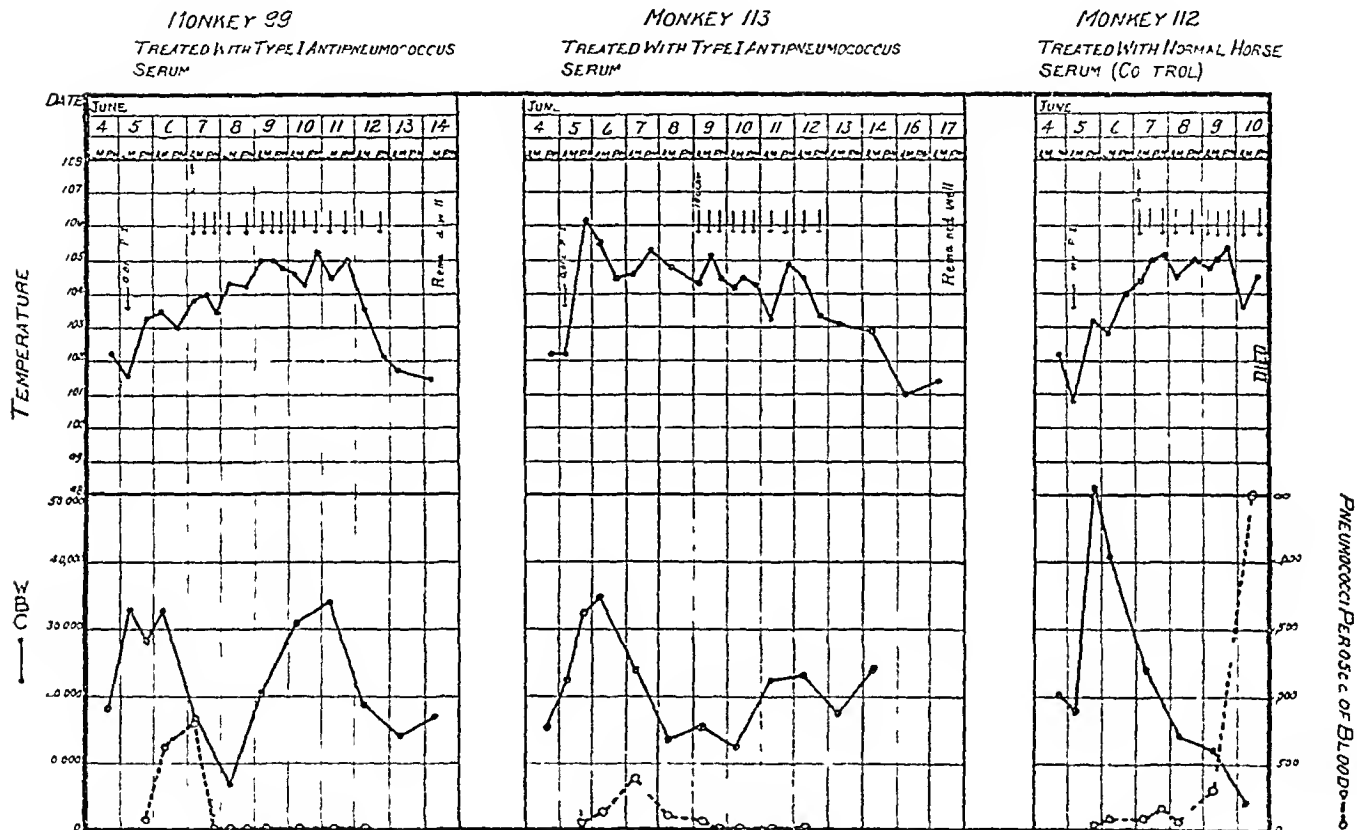


Chart 7—Pneumococcus type I pneumonia in monkeys. Two monkeys (99 and 113) were treated with type I serum and recovered. The control, monkey 112, received normal horse serum and died.

may be several: (1) patients are not treated early enough, (2) the serum may not be sufficiently potent, (3) the serum is given in too small doses, or (4) the serum is not given frequently enough.

Before passing on to a discussion of derivations of serum, something should be said about type II antipneumococcus serum. Theoretically, type II serum should be just as effective as that for type I, but in addition to the practical defects encountered in the use of type I serum, other problems are encountered in pneumococcus type II pneumonia. In the first place, it is almost impossible to develop a serum equal in potency

to that of a good type I serum, in the second place, pneumococcus type II when growing in the body of an animal or man produces much more specific soluble substance than pneumococcus type I. In view of the ability of this substance to neutralize homologous serum, it is obvious that type II infections will require a great many more antibodies than type I infections.

MONKEY 45

MONKEY 79

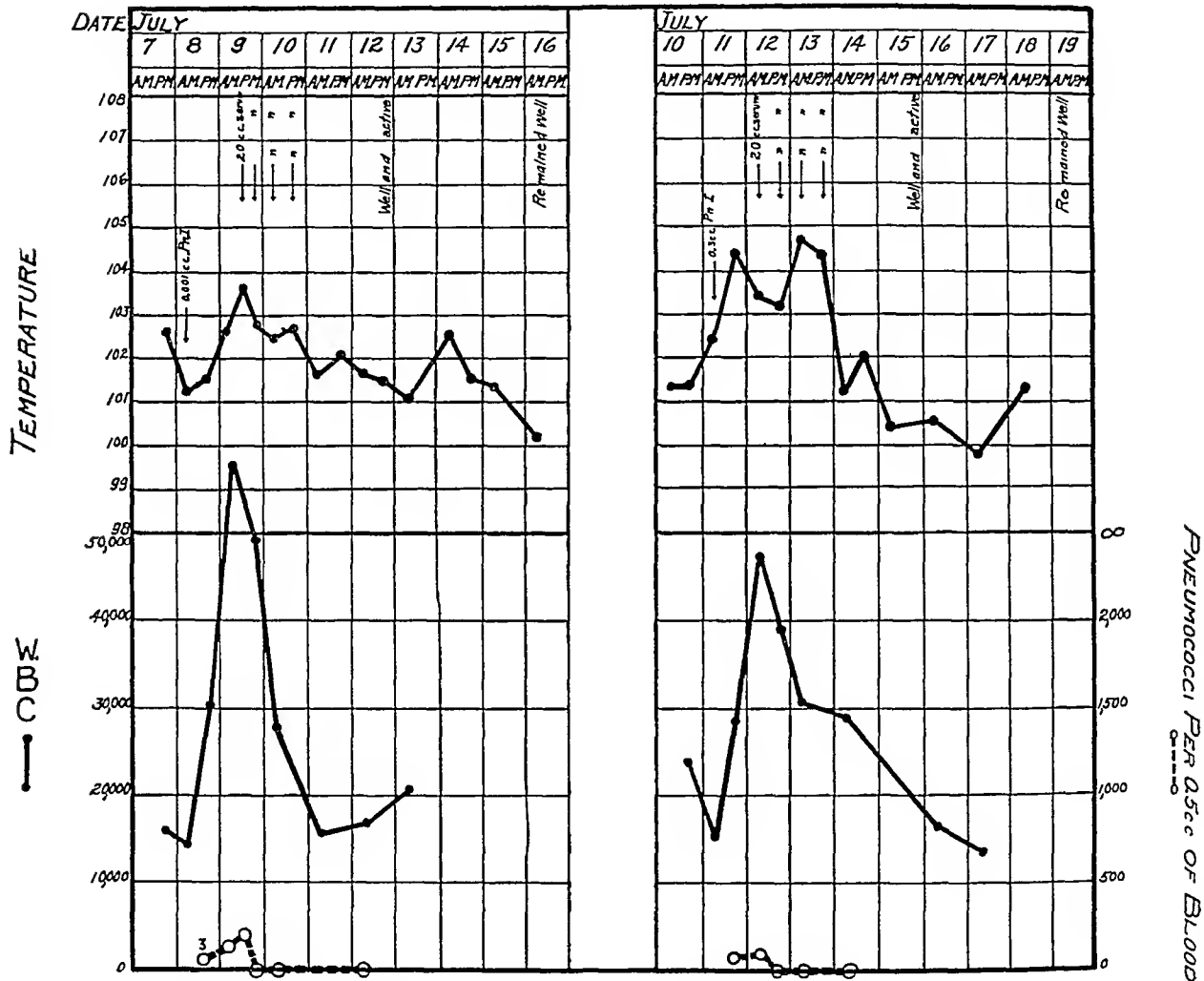


Chart 8—Abortive type I pneumonia in monkeys produced by intensive treatment with type I serum

Cole and his co-workers at the Rockefeller Hospital tried type II antipneumococcus serum on patients with type II pneumonia and were unable to demonstrate any therapeutic effect on the course of the disease. During the winter of 1926, however, Dr. William H. Park of the New York City Board of Health immunized a horse against pneumococcus type II and obtained a serum of such potency that 0.2 cc would protect a mouse against 0.2 cc of pneumococcus type II culture. In other

words, the potency of this serum was equivalent to that of the best type I antipneumococcus serum

Last winter my co-workers and I had an opportunity to test this serum on a number of patients with type II pneumonia at Bellevue Hospital. Chart 9 shows the variations in temperature of a patient with type II pneumonia treated on the third day of the disease with type II antipneumococcus serum. This patient had a sterile blood culture. One injection of serum, however, was sufficient to establish a reserve of immune bodies

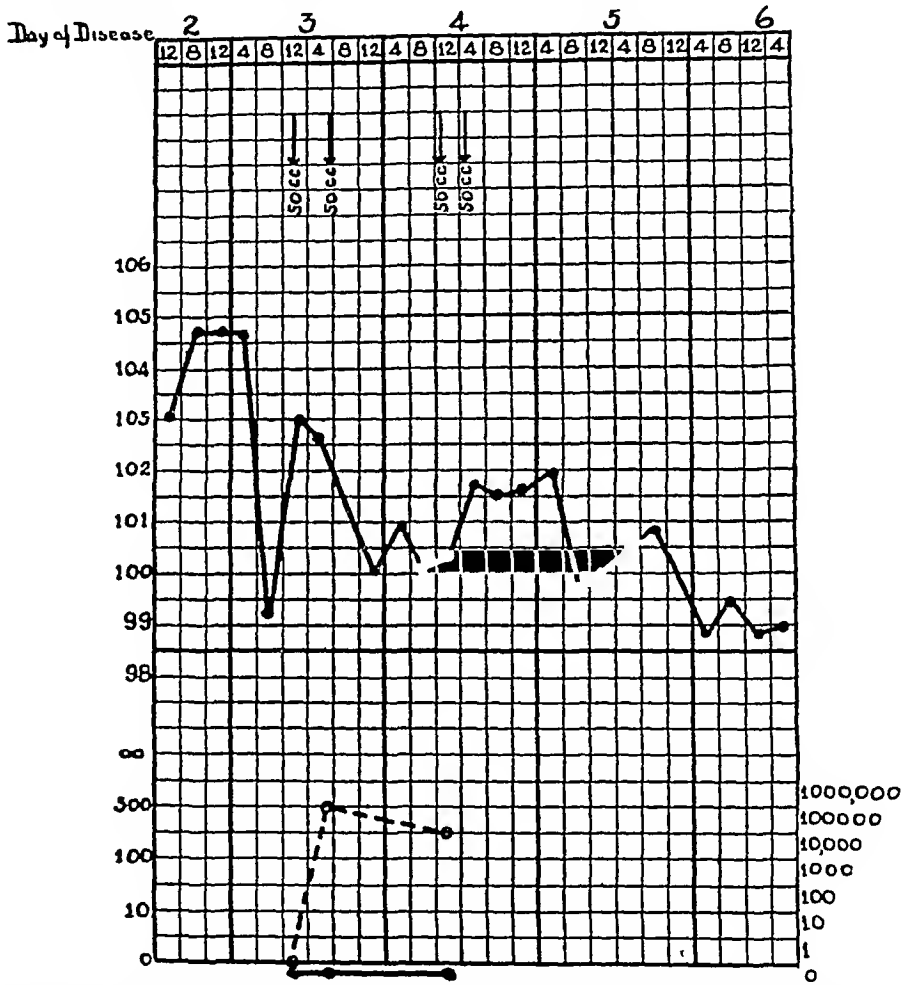


Chart 9—Variations in temperature of a patient with pneumococcus type II pneumonia treated with type II antipneumococcus serum

in the patient's blood. The patient received four other injections on the same day and two injections on the following day. The temperature came down at the beginning of the fifth day.

Chart 10 shows the variations in temperature in an interesting case of type II infection which was characterized by heavy septicemia on the second day. Two injections of serum brought about a complete sterilization of the blood, and after three more injections on the following day a balance of specific antibodies made their appearance in the blood and proceeded until the temperature reached normal.

Examples of this kind lead us to feel that in a certain number of patients with type II pneumonia in which treatment is begun early, the type II serum exercised a definite therapeutic effect. Unfortunately, the number of patients treated was not sufficiently large to furnish reliable statistical evidence.

In view of these obvious difficulties in the general use of antipneumococcus serum, it was natural that immunologists should make efforts to concentrate and purify type I serum. Gay and Chickering²⁰ were the first to show that the immune bodies in pneumococcus serum could be removed by chemical methods. By mixing a solution of pneumococcus

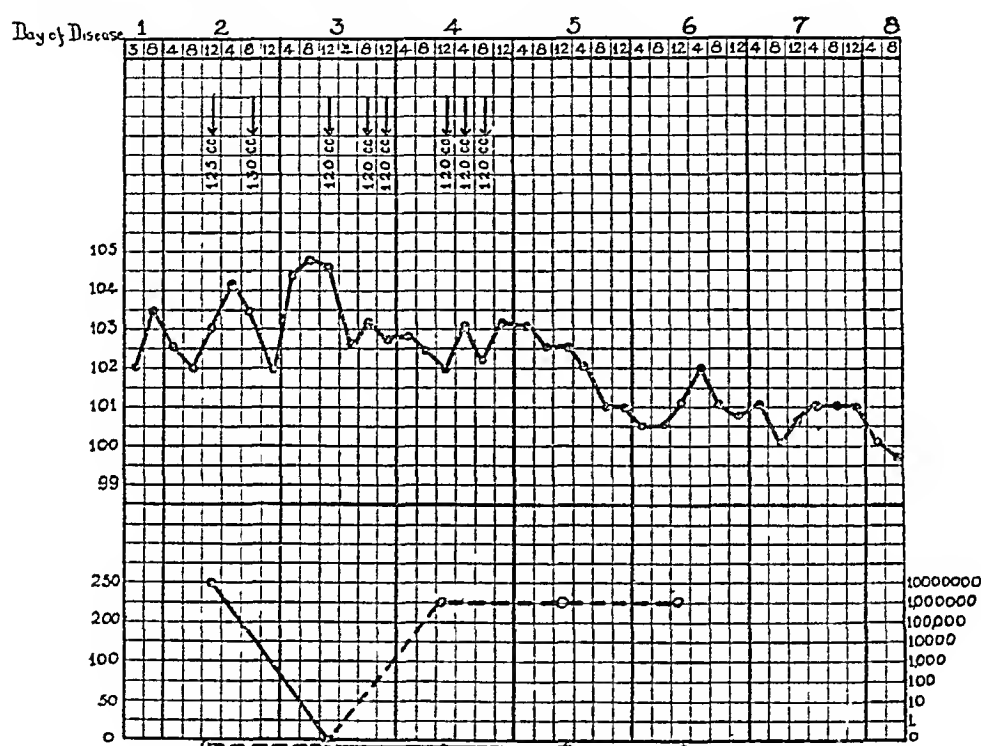


Chart 10—Variations in temperature of a patient with pneumococcus type II pneumonia treated with type II antipneumococcus serum. Heavy septicemia apparently controlled by serum.

bodies and homologous antiserum, a voluminous precipitate resulted which contained practically all the immune substances of the serum. The immune bodies contained in this precipitate were then extracted in a diluted alkaline solution at 42 C. The resulting water-clear extract possessed the power to protect animals against pneumococcus infection, and it also contained other demonstrable antibodies, such as agglutinins and precipitins. By this method, a large proportion of the antibodies could be concentrated in a volume from one-fifth to one-tenth that of

the original serum, but the product thus obtained was not stable, and the technic involved was so laborious that the authors considered the method impracticable for therapeutic purposes

HUNTOON'S PNEUMOCOCCUS ANTIBODY SOLUTION

In 1921, Huntoon²¹ published a series of articles which had to do with the removal of pneumococcus antibodies from antipneumococcus serum. The method used by Huntoon was somewhat like that employed by Gay and Chickering, but in one respect fundamentally different. The precipitate obtained by Gay and Chickering was derived in great part from the serum proteins, hence, their solutions contained serum and gave serum reactions. Huntoon used only formed antigens which could be washed free from serum. This method eliminated to all practical purposes all the serum constituents with the exception of the immune bodies themselves. Huntoon also introduced another innovation into the specific treatment of patients with pneumonia. His horses were inoculated against pneumococcus types II and III, as well as against type I. The serum was, therefore, trivalent, containing immune bodies against the three fixed types of pneumococcus.

The actual method of preparation of Huntoon's antibody solution is as follows:

Pneumococci of the three fixed types are exposed to the action of a large amount of an antipneumococci immune serum, multivalent for types I, II and III. The sensitized organisms are removed by centrifugalization, carrying the attached antibody with them. The bacteria are then washed free from serum by repeated changes of salt solution. Finally, they are emulsified in salt solution containing 0.25 per cent sodium bicarbonate and are heated to 55 C. for from thirty minutes to one hour. The emulsion is again centrifugalized, and the supernatant removed, chilled, recentrifugalized, and finally filtered through a filter candle.

Huntoon's antibody solution is a water clear product with a total nitrogen content of only 0.035 mg. per cubic centimeter. It gives a negative biuret reaction, however, although no serum proteins are demonstrable by chemical means, but they are detectable in a small amount by sensitization tests on guinea-pigs. Huntoon's solutions are stable when preserved at low temperatures.

Huntoon's antibody solution usually contains a high content of protective bodies against pneumococcus type I, 0.2 cc. usually protecting against 0.1 cc. of a virulent type I culture. Its protective power against types II and III is not so marked. In many lots, 0.2 cc. of antibody will protect against 0.01 cc. of type II culture, but even at this figure it is only one-tenth as potent for type II as for type I. Against type III, the potency is even lower, the best lots rarely protecting against more than

21 Huntoon, F. M., Masucci, P., and Hannum, E. *J. Immunol.* 6: 185, 1921.

0.001 cc of virulent type III culture. It can readily be seen that, theoretically at least, Huntoon's solution possesses great advantages over the original antipneumococcus serum. Practically free from animal protein, it eliminated at once the danger of anaphylactic reactions and the discomforts of serum sickness. Furthermore, it contained antibodies against all three of the fixed types of pneumococcus and could be employed at once without waiting for a bacteriologic examination of the sputum.

In the first place, it seemed desirable to test the value of Huntoon's solution on experimental pneumonia in monkeys, just as we had previ-

Monkey 91

Monkey 92

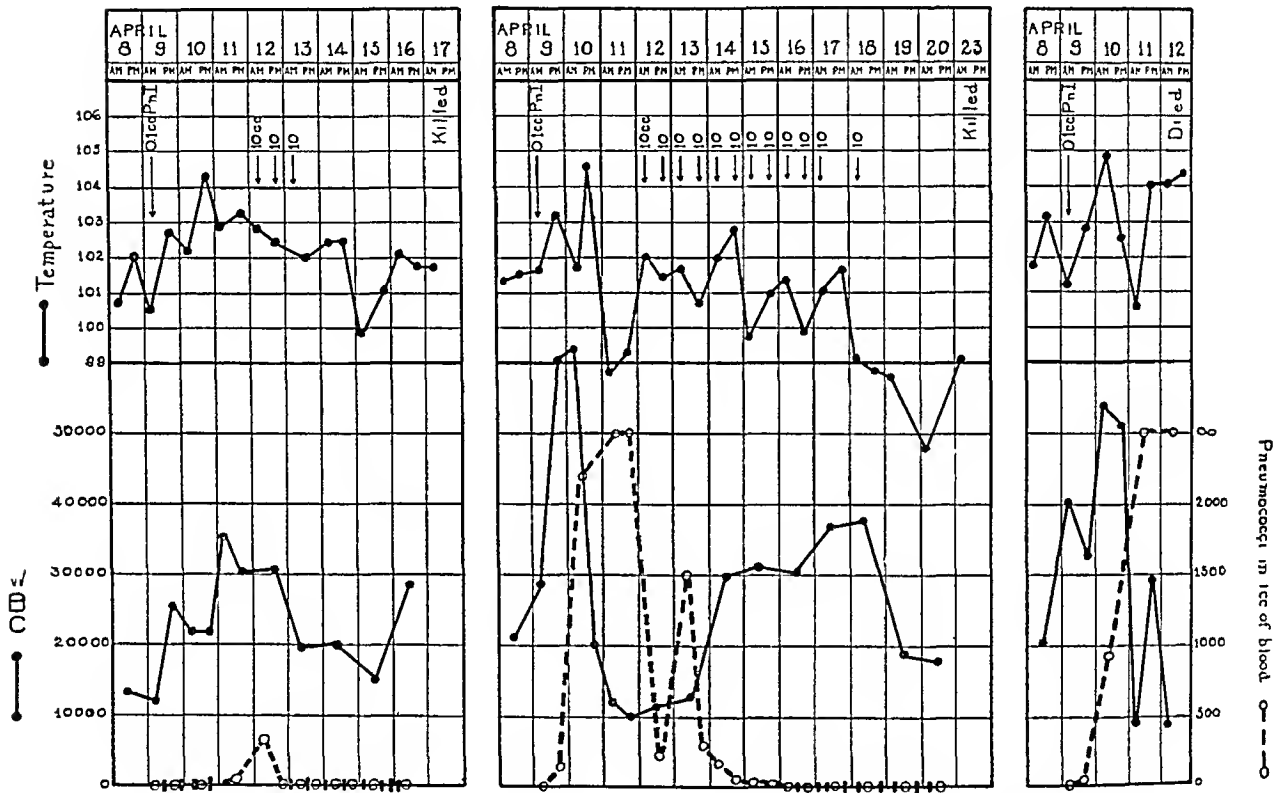
Monkey 93
Control

Chart 11—Treatment of monkeys with pneumococcus type I pneumonia with Huntoon's antibody solution

ously tested type I serum. Chart 11 shows the results for three monkeys subjected to experimental type I pneumonia. Each monkey received a lethal dose of type I culture intratracheally, and all promptly developed symptoms and signs of pneumonia and septicemia. Seventy-two hours after infection monkeys 91 and 92 received their first injection of Huntoon's antibody solution. The treatments were continued twice a day as long as either monkey showed symptoms. It will be seen from the charts that in both instances the injections quickly drove the pneumococci from the blood and, following this, effected a rapid recovery in

Monkey 134

Monkey 135

Monkey 136

Monkey 137

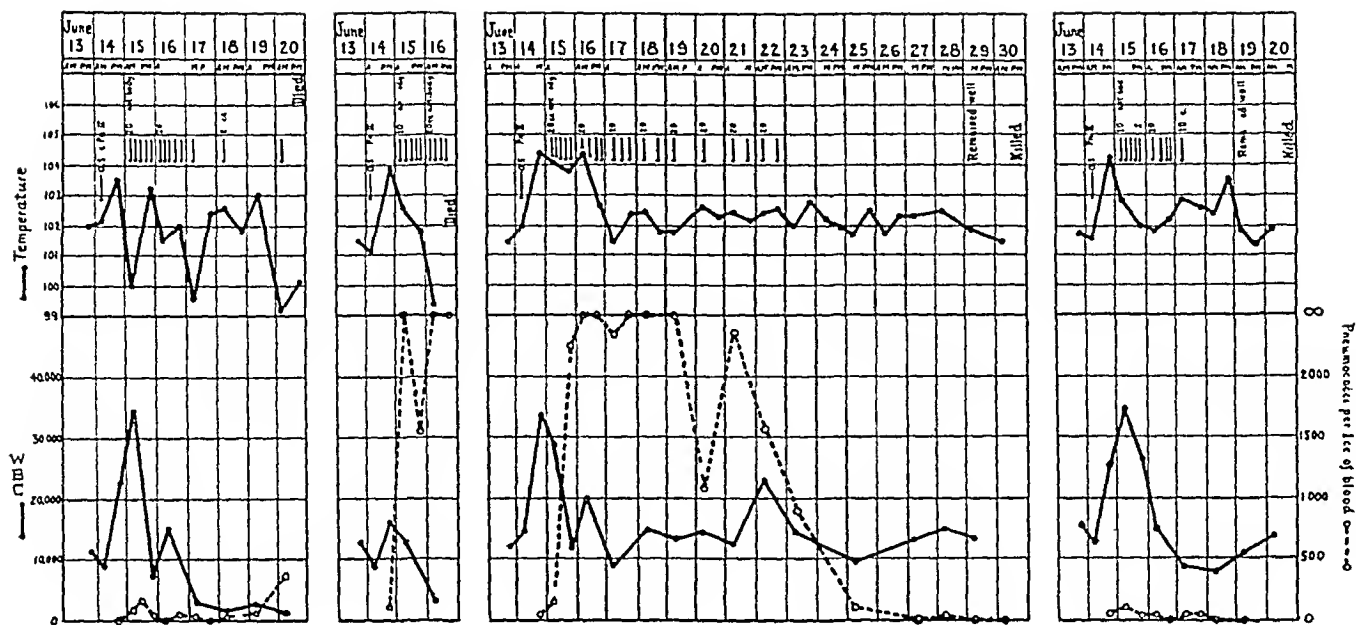


Chart 12—Treatment of monkeys with pneumococcus type II pneumonia with Huntoon's antibody solution

Monkey 138

Monkey 141

Monkey 142

Monkey 143

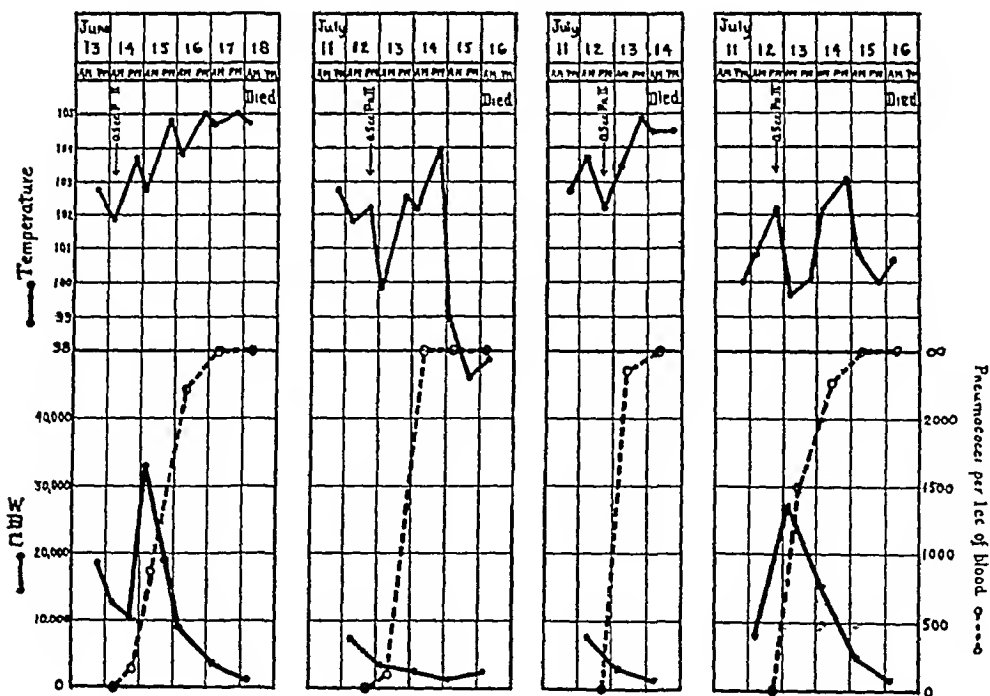


Chart 13—Pneumococcus type II pneumonia in monkeys that were not given antibody solution

both monkeys The control monkey received no antibody and died on the fourth day with pneumonia and pneumococcus septicemia From this experiment, it was clear that Huntoon's solution was just as efficacious in type I pneumonia as type I serum had been

Our next experiment was concerned with the treatment of monkeys that had experimental type II pneumonia with Huntoon's solution (charts 12 and 13) Eight monkeys were subjected to experimental

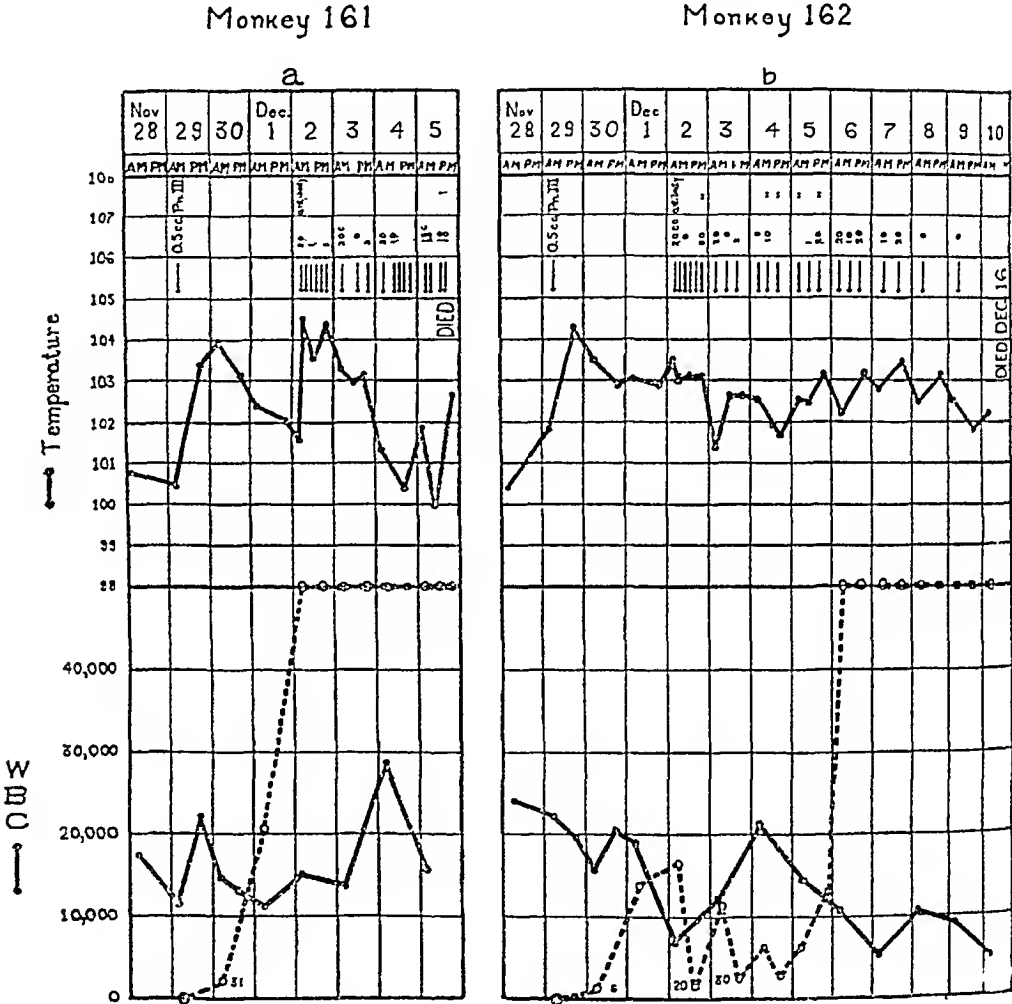
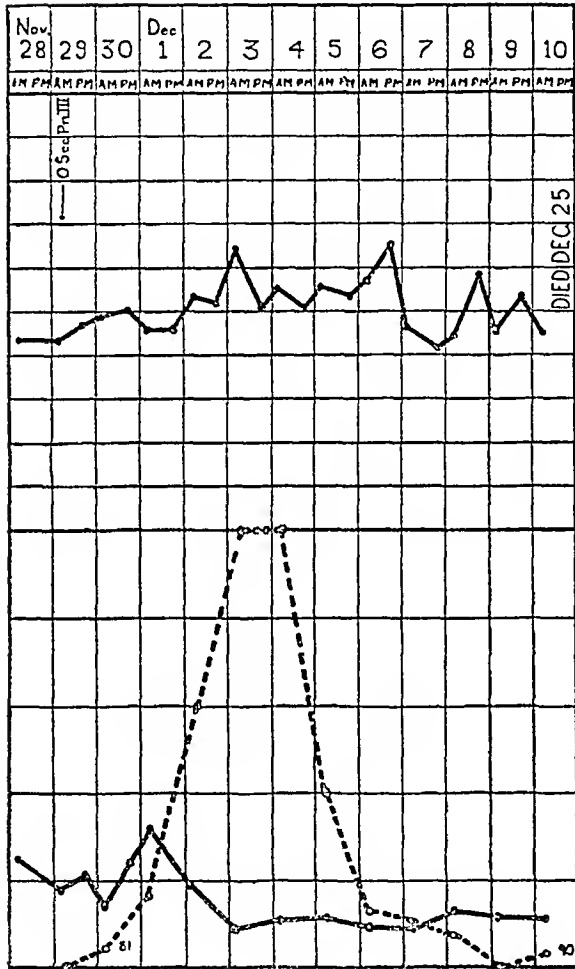


Chart 14—Treatment of monkeys with pneumococcus

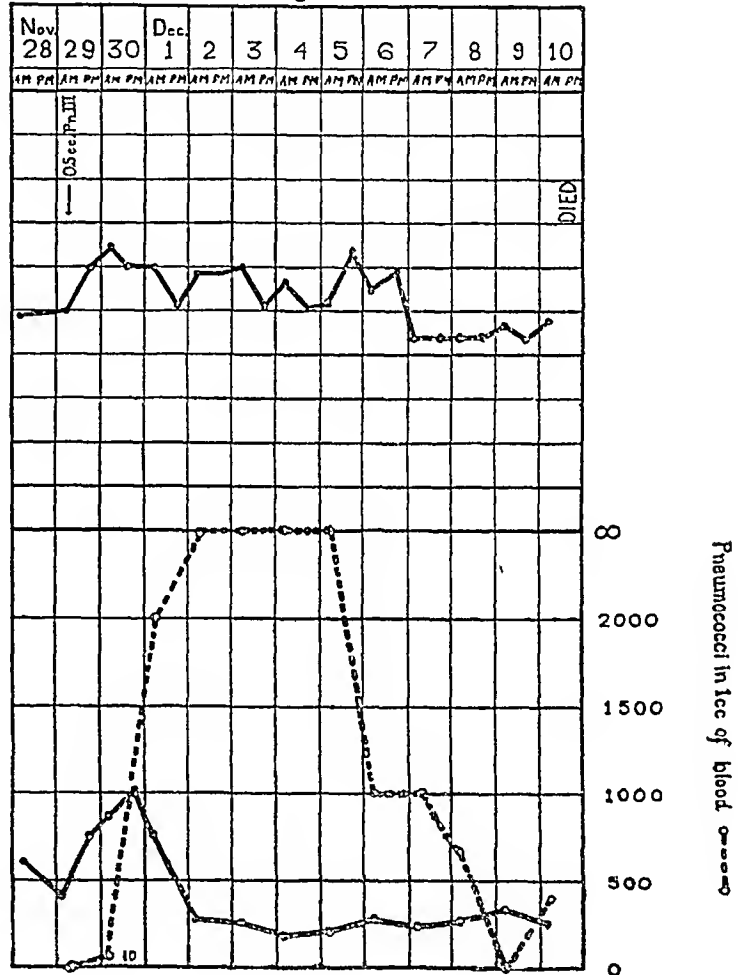
type II pneumonia by injecting a lethal dose of type II pneumococcus culture intratracheally Twenty-four hours after injection the monkeys were sick At this time, four of the monkeys (chart 12) were started on treatment with Huntoon's antibody solution, each monkey receiving 20 cc intravenously four or five times a day Larger doses were used than in the case of type I pneumonia for the reason that the antibody solution had less potency against type II than against type I pneumonia As will be seen from the two charts, the four monkeys that did not

receive serum all died of pneumonia and septicemia from three to five days after the infection. Two of the monkeys that received serum recovered and two died. In the two that recovered, the antibody solution appeared to have the same effect that it had had in the type I infections, namely, it removed the pneumococci from the blood stream, but it should be noted that this was not done in so striking a manner as in the type I cases. In the other two monkeys treated septicemia persisted in spite of

Monkey 163
Control
C



Monkey 164
Control
d



type II pneumonia with Huntoon's antibody solution

treatment, and the monkeys died. The four controls (chart 13) died with pneumococcus type II pneumonia and septicemia.

As Huntoon's solution contained some protective substance against type III pneumonia, an experimental test was performed on monkeys with type III pneumonia (chart 14). Four monkeys (161, 162, 163 and 164) were given a lethal dose of type III culture intratracheally. All four promptly developed symptoms of pneumonia. Two of the monkeys, numbers 207 and 208 were started on Huntoon's solution about seventy-

two hours after injection. From three to five injections of from 10 to 20 cc each were given daily thereafter. In spite of this treatment both monkeys died with pneumonia and septicemia, one on the seventh day and the other on the twelfth day of their disease. The control monkeys (163 and 164) also died of pneumonia and septicemia.

From these experiments on monkeys, we were justified in concluding that Huntoon's polyvalent antibody solution was of great value in type I pneumonia, of some value in type II pneumonia and without value in type III pneumonia. As will be shown presently, these results tallied exactly with the results obtained in the treatment of patients with these types of pneumonia.

During the winters of 1920, 1921 and 1922, Huntoon's antibody solution was extensively tried out in the wards of Bellevue Hospital.²² In six medical wards, every patient with lobar pneumonia who was

TABLE 3—Comparison of Death Rate in Series of Treated Patients and in Control Series

| Type of Pneumococcus | Antibody Wards | | | Control Wards | | |
|----------------------|----------------|--------|---------------|---------------|--------|---------------|
| | Cases | Deaths | Rate per Cent | Cases | Deaths | Rate per Cent |
| I | 158 | 21 | 13.3 | 162 | 36 | 22.2 |
| II | 83 | 23 | 27.7 | 67 | 27 | 40.3 |
| III | 73 | 29 | 39.7 | 60 | 24 | 40.0 |
| IV | 110 | 18 | 16.4 | 121 | 29 | 24.0 |
| Total pneumococcus | 424 | 91 | 21.4 | 410 | 116 | 28.3 |
| Streptococcus etc. | 48 | 24 | 50.0 | 35 | 12 | 34.3 |
| Unclassified | 36 | 14 | 38.8 | 47 | 20 | 42.5 |

admitted, regardless of type, was treated with antibody solution, in the other six wards all cases of pneumonia were typed and the patients were carefully observed, but no antibody solution or other serum treatment was employed. Altogether, 424 patients with pneumococcus pneumonia were studied in the antibody wards and 410 in the control wards. Practically all of the patients in the antibody wards received antibody. The only exceptions were a few patients who died or had their crisis before antibody could be administered. The treated patients, however, have been included in the figures presented. Table 3 shows the results obtained. The most striking results, as in the monkeys, were observed in the type I infections. In 158 cases in which the patients were treated with antibody, the death rate was only 13.3 per cent, while in 162 control cases there was a death rate of 22.2 per cent. In type II infections the figures were not so striking, but there was a difference. In eighty-three type II cases, in which the patients were treated with antibody solution, the death rate was 27.7 per cent as compared with 40.3 per cent in the

²² Cecil, R. L. and Larsen, N. P. Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia, J. A. M. A. 79:343 (July 29) 1922.

control wards. Patients with type III infections were not benefited by antibody treatment, the death rate for the two groups being practically the same (39.7 vs. 40 per cent).

One of the most interesting and unexpected features of this therapeutic experiment was the effect of Huntoon's solution on patients with the so-called type IV pneumonia. One hundred and ten patients with pneumococcus type IV pneumonia who were treated with antibody, showed a death rate of 16.4 per cent, while 121 type IV controls had a mortality of 24 per cent. The probable explanation of this difference will be given presently.

When only cases in which the patients were treated early were counted, more striking figures were obtained. In table 4, the results

TABLE 4—*Death Rates for Patients with Pneumococcus Pneumonia Receiving Antibody Solution Intravenously Within Forty-Eight Hours of Onset of the Disease. Control Shows Death Rate for Patients with Pneumococcus Pneumonia Admitted to Control Wards Within Forty-Eight Hours of Onset of the Disease*

| Type of Pneumococcus | Cases Treated with Antibody | | | Control Cases | | |
|-------------------------|-----------------------------|--------|-------------------------|---------------|--------|------------------------|
| | Cases | Deaths | Death Rate, per Cent | Cases | Deaths | Death Rate per Cent |
| I | 56 | 5 | 8.9 | 68 | 16 | 23.5 |
| II | 24 | 5 | 20.8 | 25 | 8 | 32.0 |
| III | 10 | 1 | 10.0 | 19 | 7 | 36.8 |
| IV | 24 | 4 | 16.6 | 45 | 11 | 24.4 |
| Total | 114 | 15 | 13.1 | 157 | 42 | 26.7 |

for patients that were treated with antibody solution within forty-eight hours of the onset are compared with those for the controls who were admitted to the hospital within forty-eight hours of the onset of the disease. In fifty-six patients with cases of early type I pneumonia who were treated with antibody, the death rate was only 8.9 per cent, sixty-eight controls admitted early had a mortality of 23.5 per cent. The death rate for twenty-four patients with type II pneumonia who were treated early was only 20.8 per cent as compared with 32 per cent in the controls. Even in the type III group the treatment appeared to have some effect, but the number of cases was too small to furnish reliable information.

The intravenous injection of Huntoon's antibody solution as originally prepared was practically always followed by a sharp thermal reaction from twenty to forty minutes after the injection. The patient began to shiver and soon had a severe chill. There was considerable cyanosis and dyspnea, and the patient often manifested extreme anxiety. The chill lasted from fifteen to thirty minutes. At its conclusion, the temperature showed a rise of 2 or 3 degrees, in rare instances even more. The high temperature usually persisted for only a short time (from thirty to sixty minutes). After that, there was a rapid fall, accompanied by profuse perspiration. These foreign protein reactions usually fol-

lowed each injection of antibody, but they tended to become less severe with each paroxysm. In three cases, the reaction following the injection of antibody appeared to be the immediate cause of death. In these three patients, the symptoms were severe chill, followed by high fever, delirium, cyanosis, dyspnea, rapid, weak pulse, diaphoresis, congestion of the lungs, coma and death.

As one reviews this experiment in the light of further knowledge which has been gleaned during the five years since the experiment was carried out it is obvious that we were obtaining something more than a purely specific effect. This is shown in the type IV group in which the

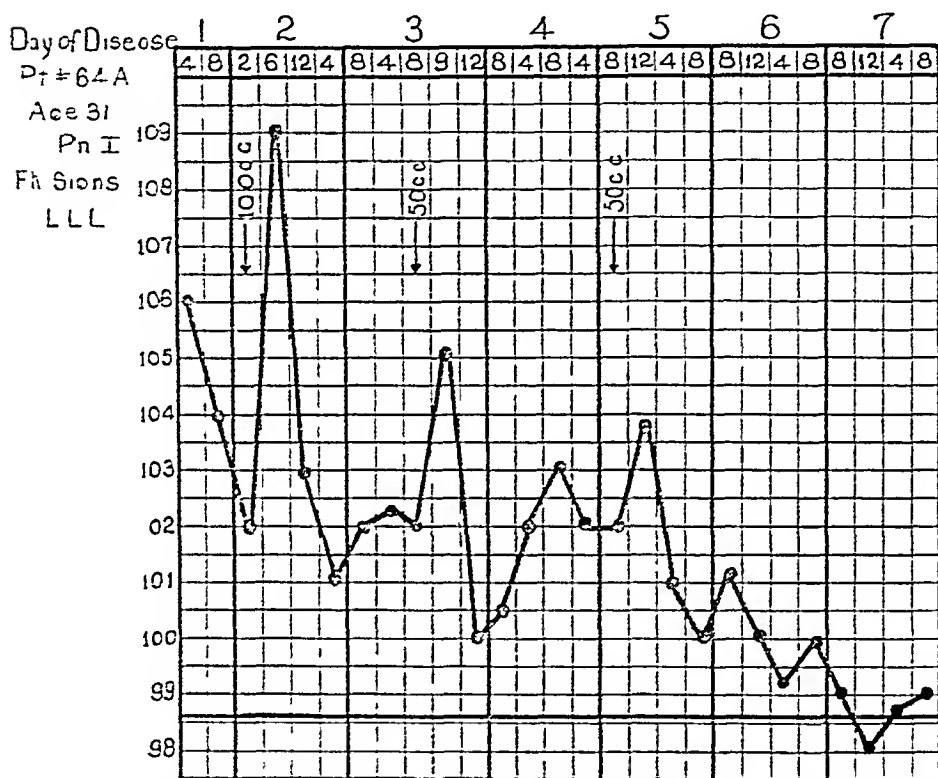


Chart 15—Variations in temperature of a patient with pneumococcus type I pneumonia treated with Huntoon's antibody solution

death rate was reduced to 16.4 per cent in treated patients as compared with 24 per cent in the untreated group. Undoubtedly, the specific antibodies contained in Huntoon's solution played an important part in the reduction of the death rate in types I and II pneumonia as the sudden and spectacular termination of symptoms after some of the thermal reactions which followed injections of antibody clearly indicates that the shock reaction itself was a therapeutic agent of considerable value in the treatment of these patients, in other words, the thermal reaction was a two-edged sword. It produced a brilliant therapeutic effect in some instances and was undoubtedly beneficial to the patient in most cases but

the occasional fatalities which occurred after this mode of treatment rendered it too dangerous a weapon to be used. If there had been some method of controlling the serum, we could have continued to make use of its beneficent qualities, but there was no way of telling whether a patient would react with a mild or a severe chill. Chart 15 shows the variations in temperature of a patient with type I pneumonia and shows well the characteristic thermal reactions. Treatment was started on the second day of the disease. Three intravenous injections were given and each was followed by a thermal reaction. Following the third reaction the patient's temperature returned to normal and remained there.

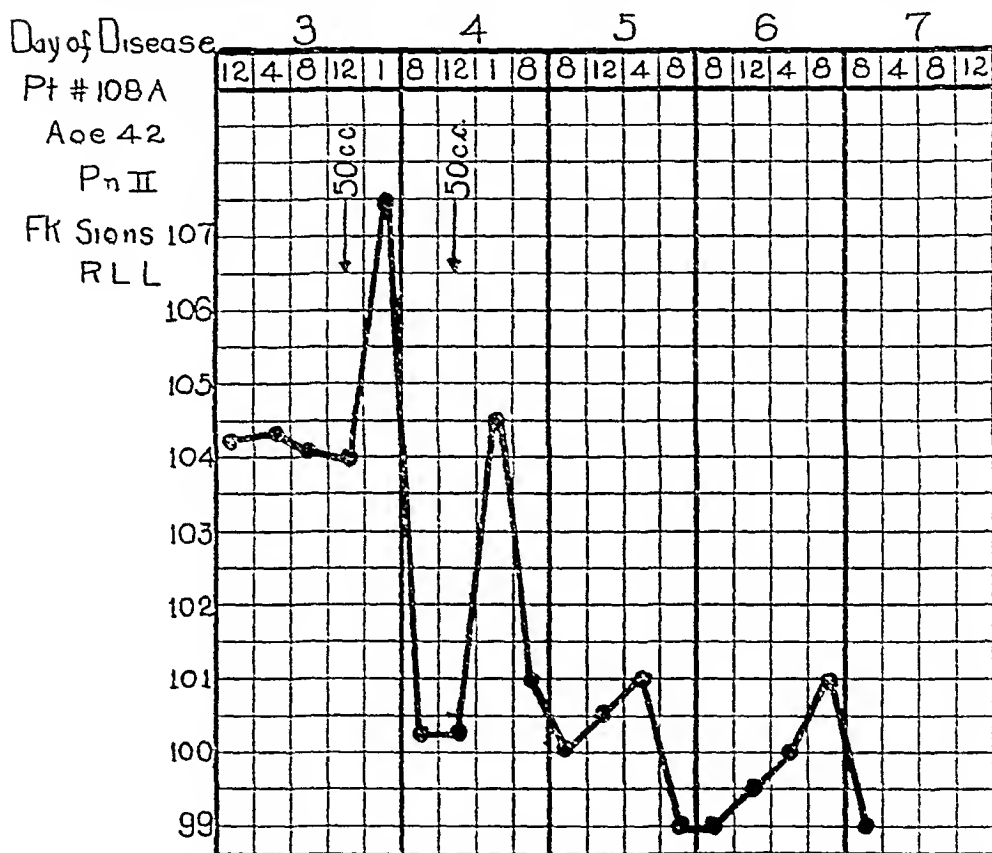


Chart 16—Variations in temperature of a patient with pneumococcus type II pneumonia treated with Huntoon's antibody solution

Chart 16 shows variations in the temperature of another patient treated with intravenous injections of antibody solution. This was a type II infection in which the first injection of antibody was given on the third day of the disease. Two injections of the solution sufficed to bring the temperature down to normal and to effect a rapid recovery. The reactions following the injections did not differ in any respect from those seen in the cases of type I pneumonia.

In some instances Huntoon's solution appeared to have some clinical effect on patients with type III pneumonia though the statistics for cases of type III pneumonia were not encouraging except when the injections were given early in the disease. Chart 17 shows the variations

in the degree of temperature of a patient with type IV pneumonia in which the intravenous injection of antibody produced a sharp reaction and apparently aborted the disease

The next problem that presented itself was to obtain, if possible, the beneficial effect of Huntoon's solution without the disadvantage of the reactions. The simplest way to avoid the reactions was naturally to inject the solution subcutaneously instead of intravenously. Larger doses of antibody were employed for the subcutaneous treatment, from 100 to 200 being the initial dose, and in severe cases even 300 cc was often given at one time. The average amount administered per case was 650 cc. This method of administering antibody was tried in the wards of Bellevue Hospital on alternate patients during the winters of 1922 and

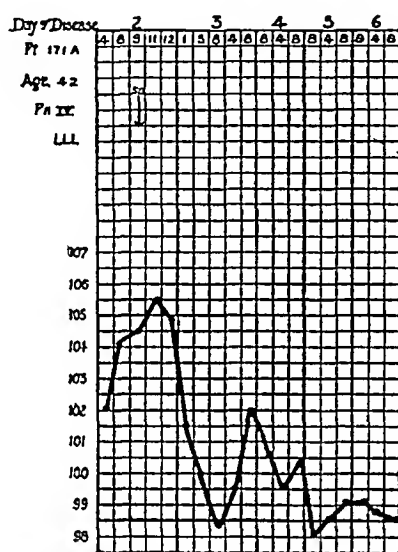


Chart 17—Variations in temperature of a patient with pneumococcus type IV pneumonia treated with intravenous injections of Huntoon's antibody solution

1923, and 1923 and 1924. The results were rather disappointing.²³ The subcutaneous method of treatment eliminated the chill, but appeared to have little effect on the course of the disease. The death rate for all types was almost as high for treated patients as for untreated controls. When only the early cases were compared, there appeared to be some difference. In table 5 the results for all patients with pneumococcus pneumonia who received antibody subcutaneously within forty-eight hours after the onset of the disease are compared with those for patients with pneumococcus pneumonia who were admitted to the control wards within forty-eight hours of the onset of the disease. There appears to have been beneficial effect, but the groups are small.

²³ Cecil, R. L., and Baldwin, H. S. *J. Pharmacol. & Exper. Therap.* **24** 1, 1924.

In the meantime, Dorothy Rhoades ²⁴ had made a study of the fate of pneumococcus protective antibodies when injected into normal animals and man. She found that when pneumococcus antibodies are injected intravenously in a normal rabbit or man, protective bodies against pneumococcus type I are readily demonstrable in the circulating blood immediately after the injection and persist there for a variable period which may be two weeks or longer. On the other hand, she found that in animals injected subcutaneously with solutions of pneumococcus antibody, a certain amount of protective substance was usually demonstrable in the blood, but that in some cases antibodies do not make their appearance in the blood. The reason for this variation was not found.

TABLE 5—*Death Rates for All Patients With Pneumococcus Pneumonia Receiving Antibody Solution Subcutaneously Within Forty-Eight Hours of Onset of the Disease. Control Shows Death Rate for Patients with Pneumococcus Pneumonia Admitted to Control Wards Within Forty Hours of Onset of the Disease, 1923 and 1923-1924 Series*

| Type of Pneumococcus | Cases Treated with Antibody | | | Control Cases | | |
|-------------------------|-----------------------------|--------|-------------------------|---------------|--------|-------------------------|
| | Cases | Deaths | Death Rate, per Cent | Cases | Deaths | Death Rate, per Cent |
| I | 23 | 4 | 17.3 | 23 | 6 | 26.0 |
| II | 13 | 5 | 38.4 | 27 | 15 | 55.5 |
| III | 7 | 4 | 57.1 | 21 | 10 | 47.5 |
| IV | 40 | 7 | 17.5 | 28 | 8 | 28.0 |
| Total | 83 | 20 | 24.0 | 99 | 39 | 39.2 |

Realizing the serious objection which the thermal reactions presented to the general use of solution of pneumococcus antibody, Huntoon had been trying to eliminate the chill-producing substance from his extract, after considerable experimentation, he succeeded in removing the greater part of it without decreasing in any way the potency of his product. The antibody solution now obtainable in the market can usually be administered intravenously without causing a chill, particularly if doses of 50 cc. are adhered to, large doses, from 100 to 150 cc. are still apt to produce a chill, and unfortunately, the large doses are often needed. Indeed, I doubt if the protective substance against types II and III pneumococcus in Huntoon's solution is sufficient to affect materially the course of a severe infection, that is, without causing a chill, if the dose is large enough to cause a chill, it may have a favorable effect not only on fixed types, but even on type IV infections. What the solution of antibody now needs is increased concentration. In a highly potent form it would be an almost ideal product for the specific treatment of patients with the fixed types of pneumococcus pneumonia.

24 Rhoades, D. Hyg. Tab. Bull., no. 141, 1925, p. 31.

FELTON'S CONCENTRATED ANTIPNEUMOCOCCUS SERUM

In 1924, Felton²⁵ published his first report on the isolation and concentration of the specific antibodies of antipneumococcus serum. In preliminary tests, Felton found that the protective substance was always associated with the water-insoluble fraction of serum, that is, the globulin. After various experiments, Felton²⁶ found that the largest return of immune bodies could be obtained from antipneumococcus serum by simply diluting one part of serum in ten parts of water. Taking advantage of this fact, he was able to isolate the specific antibodies and redissolve them in a concentrated form. The concentrate, of course, contained serum globulin in addition to the immune bodies. Actually these earlier lots of Felton's serum contained 3.5 mg of nitrogen per cubic centimeter. The technic employed by Felton was as follows:

One liter of serum is slowly poured into 15 liters of agitated, cooled distilled water, and the precipitate is allowed to settle over night in the icebox. The supernatant fluid is then syphoned off, and the flocculent precipitate is washed with the same volume of cooled, distilled water used for the precipitation. The suspension is again permitted to settle for twenty-four hours. Once more, the supernatant liquid is syphoned off and the white sediment collected by means of a Sharpless centrifuge. The compact white residue in the bowl of the centrifuge is taken out and dissolved in one-half molecular sodium chloride. If the solution is not clear, it is then passed through a Berkefeld candle. The resulting filtrate is a slightly opalescent fluid, free from sediment. By the use of this technic on a number of different antipneumococcus serums, concentrates two or three times stronger in immune bodies than the original were obtained. Even greater concentration, however, has been secured by using other solvents than sodium chloride, such as tartaric acid.

The first lots of Felton's serum were subject to the disadvantage which has already been described in connection with Huntoon's solution. Intravenous injections of even small amounts were nearly always followed by thermal reactions. Felton, however, like Huntoon, has discovered methods of eliminating the chill-producing substances. At the present time, not more than 10 per cent of patients have thermal reactions after intravenous injection, an incidence which is no higher than that following the intravenous injection of the original serum.

One of our first experiments with Felton serum was a test of its efficacy in the control of experimental pneumococcus pneumonia in monkeys. The variations in temperature and the number of white blood cells for four monkeys that were infected with lethal doses of pneumococcus type I pneumonia are shown in chart 18. Twenty-four hours after infection, three of the monkeys were started on intravenous injections of Felton's type I serum. The fourth monkey served as a control.

25 Felton, L. D. *Boston M. & S. J.* **190** 819, 1924.

26 Felton, L. D. *J. Infect. Dis.* **37** 1, 1925.

By referring to the charts, it will be seen that in the case of the three monkeys that received the serum a striking effect was produced in the course of the disease. The temperature dropped and the pneumococci disappeared from the blood, just as in a previous experiment in which the monkeys had been treated with type I serum or with Huntoon's antibody solution. The three monkeys that were treated with Felton's serum made a complete recovery while the control monkey developed a fulminating septicemia and died on the fourth day.

Monkey 308

Monkey 309

Monkey 310

Monkey 311
Control

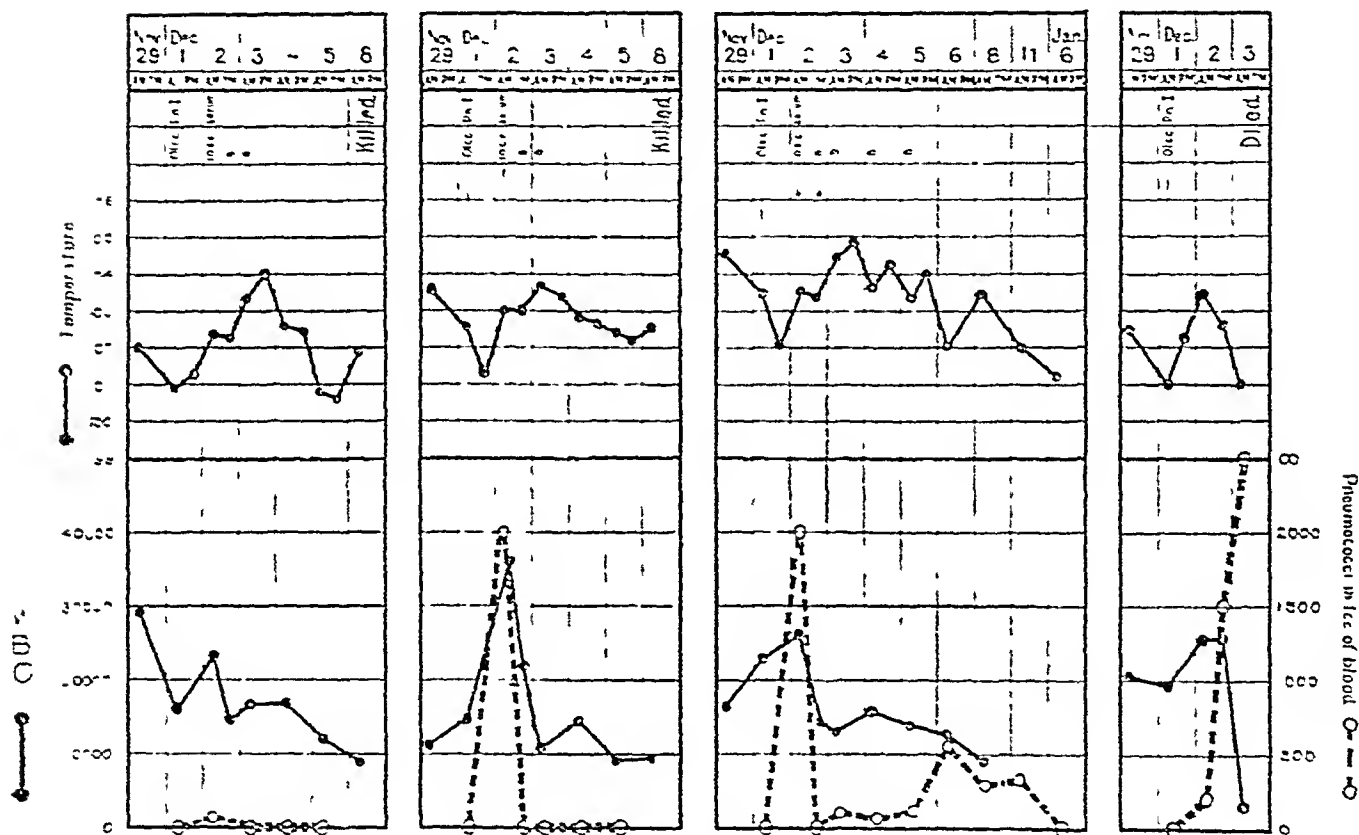


Chart 18—Three monkeys (308, 309 and 310) with pneumococcus type I pneumonia were treated with Felton's type I serum and recovered. The control (311) did not receive the serum and died.

We then began to try out the Felton serum on patients in the wards. Dr. Felton supplied us with a polyvalent serum of high potency against pneumococcus type I and a fairly high potency against pneumococcus type II. The polyvalent serum was administered intravenously as soon as the diagnosis of pneumonia was made. If bacteriologic examination revealed a pneumococcus type I or type II infection, we changed to monovalent serum either type I or type II as the case might be. If the laboratory reported pneumococcus type III or type IV, serum treatment was discontinued.

The clinical effect of Felton's serum on type I infections is often striking. Chart 19 shows the variations in temperature and the number of pneumococci per cubic centimeter of blood of patients with type I pneumonia who were treated on the fourth day with two intravenous injections of Felton's type I serum. It will be noted that on the morning of the fourth day, the patient's blood was entirely free from immune bodies. Four hours after the first injection of serum, the blood showed a large amount of protective antibodies. The two injections of 10 cc of serum were given in the evening. The patient's blood maintained a high content of immune bodies, and on the following morning the crisis occurred.

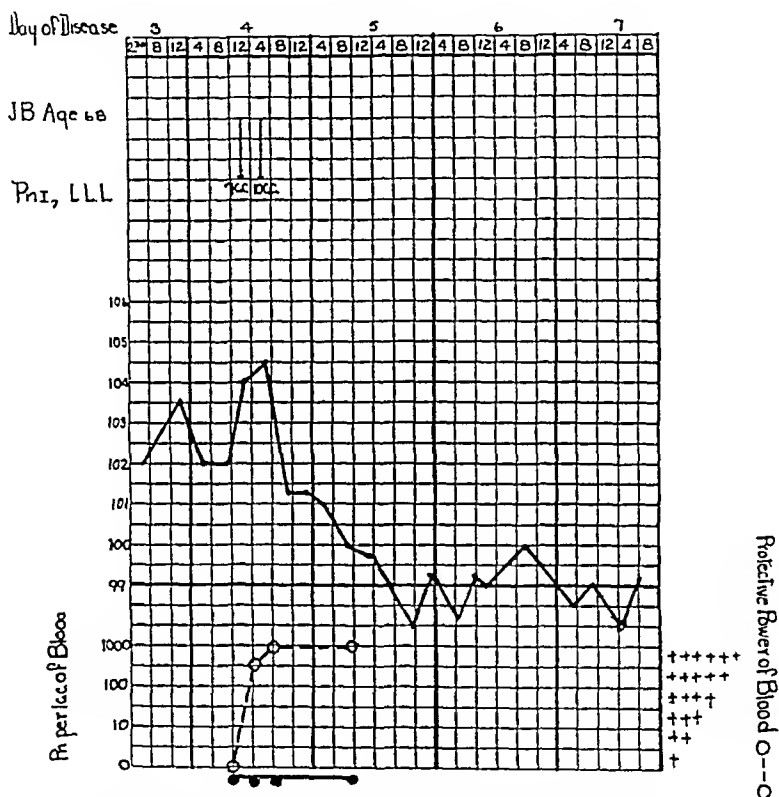


Chart 19—Variations in temperature of a patient with pneumococcus type I pneumonia treated with Felton's concentrated type I serum

In chart 20 the results are given for another patient with type I pneumonia admitted on the first day of his disease with a temperature of 102.5 F and well marked septicemia (10 colonies to each cubic centimeter of blood). At this time the blood was entirely free from immune bodies. Six intravenous injections of Felton's serum were given on the first day. On the second day the blood was sterile and contained a large amount of protective antibodies. This state of affairs continued, and on the morning of the third day the patient had a crisis.

It is evident from these charts that small doses of Felton's concentrated serum are capable of achieving the same results that are obtained

by large doses of Cole's type I serum and Huntoon's antibody solution. The temperature drops, bacteria disappears from the blood and the crisis is hastened. Similar effects have been produced in patients with pneumococcus type II pneumonia, but we have found that in the case of type II infections, it is important that treatment should be started early.

Statistical evidence concerning the value of Felton's serum is not yet convincing, as the number of patients treated has not been sufficiently large. During the past winter in Bellevue Hospital, alternate patients with pneumonia have been treated with Felton's serum.

Patients who had type I and type II infections were treated intensively, those with type III and type IV received only the initial injections.

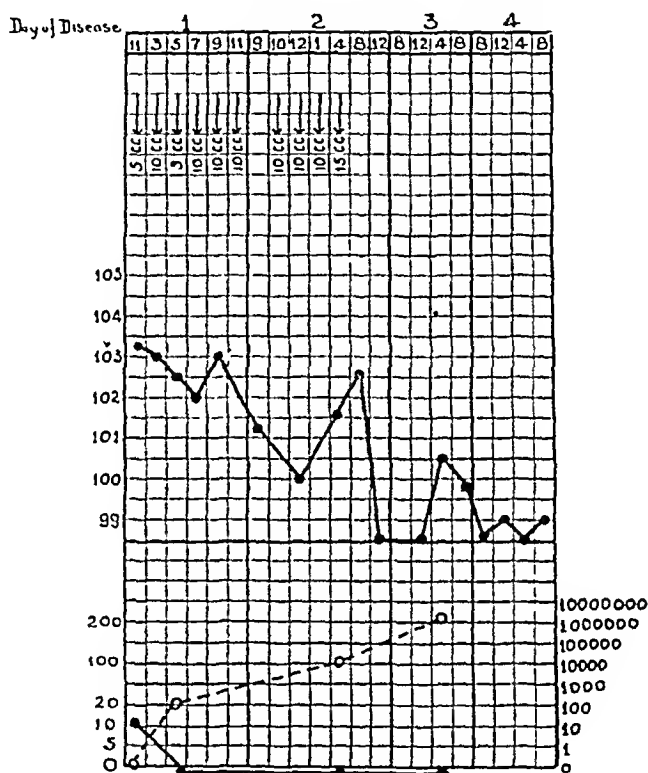


Chart 20—Variations in temperature of a patient with pneumococcus type I pneumonia with septicemia treated with Felton's concentrated type I serum

which were given before the types were determined. In table 6, patients that received serum are compared with those that did not receive any. In this table, patients dying within twenty-four hours after being admitted to the hospital have been excluded in both groups. In forty-eight cases of type I pneumonia in which the patients were treated, the death rate was 20.8 per cent, in the control group, the death rate was 29.5 per cent. In the type II group, treatment appeared not to have any effect, the death rate in the treated series being almost identical with that in the untreated series (48 per cent versus 46.1 per cent).

In table 7, patients that were treated during the first four days of their disease are compared with controls admitted to the hospital during the first four days of the disease. This table demonstrates clearly the importance of every treatment. The death rate¹ in the treated patients with type I pneumonia is only 11.1 per cent, and the patients with type II pneumonia that received serum early show a mortality of 23.3 per cent as compared with 42.1 per cent in the control cases with type II pneumonia.

Incidentally, this table illustrates the perils of statistics. Nine patients with type III pneumonia in the untreated series show a mortality

TABLE 6—*Death Rates of Patients with Pneumococcus Pneumonia Receiving Felton's Serum, Compared with Alternate Cases in Which Serum was not Given*

| Type | Treated | | | Untreated | | |
|------|---------|------|-------------------------|-----------|------|-------------------------|
| | Cases | Died | Percentage of Mortality | Cases | Died | Percentage of Mortality |
| I | 48 | 10 | 20.8 | 61 | 18 | 29.5 |
| II | 25 | 12 | 48.0 | 26 | 12 | 46.1 |
| III | 18 | 6 | 33.3 | 32 | 6 | 18.7 |
| IV | 66 | 16 | 24.2 | 43 | 14 | 32.5 |

TABLE 7—*Death Rates of Patients Treated with Felton's Serum During the First Four Days of Disease, Compared with Controls Admitted During First Four Days of Disease*

| Type | Treated | | | Untreated | | |
|------|---------|------|-------------------------|-----------|------|-------------------------|
| | Cases | Died | Percentage of Mortality | Cases | Died | Percentage of Mortality |
| I | 18 | 2 | 11.1 | 21 | 4 | 19.0 |
| II | 11 | 3 | 27.3 | 19 | 8 | 42.1 |
| III | 4 | 2 | 50.0 | 9 | 0 | 0.0 |
| IV | 28 | 6 | 21.4 | 14 | 5 | 35.6 |

rate of zero¹. Ordinarily the death rate in this type of pneumonia is 40 per cent. For some reason the patients with type IV pneumonia who receive an injection of Felton's serum show a considerably lower death rate than the control cases. This figure, however, is only slightly below the usual death rate of patients with type IV pneumonia. The death rate in the control cases of type IV pneumonia is abnormally high in this particular series.

These figures indicate clearly that Felton's serum has a definite effect on type I pneumonia, this effect being most marked when the serum is administered early. The evidence in type II pneumonia is not so convincing, but judging from the effect in individual cases in which the serum administered early has sterilized the blood and caused a clinical

improvement in the patient one would seem justified in concluding that Felton's serum will sometimes be of value in type II pneumonia, especially when administered early in the disease.

This conclusion is supported by the statistics which show a comparatively low death rate for patients treated with serum during the first four days of the disease. It must be admitted, however, that the number of cases is still comparatively small.

GENERAL SUMMARY

I shall now consider the comparative merits of these various specific agents. One thing I think is clear, and that is that the principle involved is the same in all. It has been proved by our investigations and those of others that death in pneumonia is accompanied in a large number of cases by pneumococcus septicemia and vice versa, that septicemia is usually followed by death.

In this review, instances have been presented in which the sterilization of the blood in pneumococcus type II pneumonia in man followed and seemed to be due to the administration of some form of homologous antipneumococcus serum. I have also tried to show that the presence of protective substance in the blood is of distinctly favorable import in prognosis. Protocols have been presented which show that it is possible, through the administration of pneumococcus type I or type II immune bodies, to establish a balance of protective substance in the blood of the patient. I have referred to the work of Avery and Heidelberger who have shown that the pneumococcus produces a soluble substance which has the property of absorbing or neutralizing the productive antibodies produced by the patient.

It has also been pointed out that in the blood of pneumonic patients, either with or without pneumococcus septicemia, the specific soluble substance may be present and display the same faculties for neutralizing immune bodies. The recent studies of Robertson and Sia with leukocytes and immune serum indicate that the specific protective bodies are necessary for the phagocytosis of pneumococci.

The chief function, then, of antipneumococcus serum is bacteriotropic, that is, an opsonization of the bacteria preliminary to their destruction by the leukocytes. If the blood stream is filled with "soluble substance," it is evident that the patient's own efforts to develop an adequate supply of immune bodies will often be neutralized by the soluble substance of the pneumococcus. If the immune serum is administered early and the administration continued for a sufficient length of time, the soluble substance may be neutralized and an actual balance of immune bodies established in the patient's blood. By such an achievement, the pneumococci are properly prepared for phagocytosis, and bacteremia is prevented.

The patient with pneumonia complicated by pneumococcus septicemia needs a great deal of help. The difficulty at present is that the patient often needs more help than one dares to give him with the agents at one's command. One hesitates to inject enormous quantities of horse serum into the veins of a sick man. The possibility of a chill or some unexpected antiphylactic reaction is enough to inspire the careful physician with a dread of intravenous serum therapy.

Of great importance, therefore, in the practical application of anti-pneumococcus serums are the problems of purification and concentration of the specific agent. Huntoon's pneumococcus antibody solution is almost entirely free from horse protein, but it lacks sufficient concentration. Felton's antibody extract has the concentration but lacks the entire freedom from horse protein which Huntoon's solution possesses. Both products sometimes produce a chill when large doses are injected intravenously.

Most of this discussion has dealt with the specific treatment of patients with type I and type II pneumonia, the two groups in which the outlook for a successful specific therapy is most promising. In the case of pneumococcus type III pneumonia, the serum and serum derivatives have thus far contained such small amounts of protective substance that their therapeutic value is practically nil. My co-workers and I have never been able to save monkeys with type III pneumonia, and we have been unable to sterilize the blood in the type III pneumonia of man by specific therapy. The death rate in patients with type III pneumonia who were treated with specific type III antibodies has been almost identical with that of the untreated patients. Specific therapy for type III pneumonia has little to offer at the present time.

In type IV pneumonia one is dealing, not with one group of pneumococci, but with a large number of biologically different types. In view of the type specificity of the protective substance, it is obviously impossible to make a type IV serum from a single strain of type IV pneumococcus. In Cecil and Larsen's series of patients treated with Huntoon's antibody solution, there was a decided lowering of the death rate in the treated patients with type IV pneumonia. Striking results in type IV pneumonia were also obtained by Conner²⁷ in his series treated at the New York Hospital with Huntoon's antibody solution. It is probable that the good results obtained in both of these statistics were due to the foreign protein or to (shock) reactions which occurred after the intravenous injections. The clinical results with Huntoon's antibody solution in type IV infections have not been striking since the chill-producing substances have been eliminated. It might be possible, of course, to prepare a polyvalent pneumococcus type IV serum by immunizing a horse against a number of pneumococcus type IV strains. This, however, is a problem for the future.

27 Conner, L. A. *Am J M Sc* 164 832, 1922

SUMMARY

From the evidence submitted, it is clear that antipneumococcus serum and its derivatives, when administered under the proper conditions, are capable of exerting a definite influence on the course of pneumococcus type I and type II pneumonia. A specific therapy for these two types of pneumonia is, therefore, theoretically sound. The practical application of the specific treatment of pneumonia is still handicapped, however, by certain defects in the serum itself or in the derivatives from it. Whatever the serum or serum derivative used, the necessity of early and adequate treatment cannot be too strongly emphasized. In our experimental work on pneumococcus pneumonia, the value of large doses of serum has always been strongly impressed on us.

With numerous investigators now studying pneumococcus infections, there is every reason to believe that each succeeding year will shed further light on the problem. During the past decade much progress has been made, but much more still remains to be done before a thoroughly satisfactory specific treatment is achieved.

IMMUNITY TO TUBERCULOSIS

JOHANNES HEIMBECK, M D

OSLO, NORWAY

Every year about a hundred young women begin a three year course in the nurses' training school at Ullevaal in the Municipal Hospital of Oslo. While in training, some of these young women contract tuberculosis in its different forms. To ascertain whether or not this disease was more frequent among the pupil nurses than among people in other environments, my chief, Dr Olaf Scheel, in 1924, began making Pirquet's tuberculin cutaneous tests on these nurses. Since then the investigation has continued, and this report is the result of this and other researches which have followed. The report will be divided into three parts in which the following facts will be considered: (1) the number of nurses with positive and the number with a negative reaction to the Pirquet test on entering the school, (2) the number and the classification of nurses contracting tuberculosis, (3) Can we prevent tuberculosis among nurses?

PIRQUET TEST

The reaction of the nurses to the Pirquet test on admission to the hospital will be shown in the diagram. With a few exceptions, the nurses were between the ages of 20 to 25, and all were in good health.

Thus table 1 shows that on entrance to the school 52 per cent of the pupils gave a negative reaction to the Pirquet test and 48 per cent gave a positive reaction. The results of these tests are in sharp contrast to the prevailing opinion relative to the spread of tuberculosis among civilized people. It is generally believed that practically every one is infected with tuberculosis during childhood or youth, so that a negative reaction to the Pirquet test is seldom found after the age of 20.

Extensive investigations have been made among the children in the public schools of Oslo. These have shown that at the age of 9 about 85 per cent of the children gave a positive reaction to the Pirquet test. In the country districts, the number of positive reactions was less. The general opinion has been that one seldom finds a negative reaction among the inhabitants of the cities at the age of 18. Most of the material for the nurses training school comes from the cities, the pupils having resided in the city for a longer or shorter period of time prior to entrance to the school.

* From Ullevaal, the Municipal Hospital of Oslo, Department of Internal Medicine. Dr Olaf Scheel, chief physician.

* Preliminary report given before the Interstate Post Graduate Assembly of North America, Oslo, Norway, June 11, 1927.

In order to check the results of the investigation on pupil nurses, other groups of people of the same age were tested with the Pirquet reaction. Seventy-nine medical students were examined prior to their entrance into hospitals and 222 military recruits, 47 per cent of the medical students gave negative reaction to the Pirquet test and 53 per cent gave a positive reaction, 55 per cent of the military recruits gave a negative reaction and 45 per cent gave a positive reaction. These investigations confirmed our observations on pupil nurses in that about 50 per cent gave negative reactions to the Pirquet test. The old opinion relative to the frequency of the positive Pirquet test in adult life seems to be wrong.

The question may well be asked, Why is the percentage of negative reactions so great at the age of 20? One possibility is that special conditions in the children examined may have caused a higher percentage of positive reactions than among children in general, this percentage perhaps does not increase to more than 50 before the person reaches the age of 20. This is, contradicted however, by the agreement of all the earlier

TABLE 1—*Reaction of Nurses to Pirquet Test*

| | Number of Nurses | Negative | Positive |
|-----------------|------------------|----------|----------|
| 1924 | 109 | 51 | 58 |
| 1925 | 114 | 72 | 42 |
| 1926 | 114 | 62 | 52 |
| 1927 until June | 83 | 35 | 48 |
| Total | 420 | 220 | 200 |

researches on the subject. Thus there are two outstanding facts: 1. In late childhood and youth there are nearly 100 per cent positive reactions. 2. The positive reactions fall to nearly 50 per cent at the age of 20. This must mean that the reaction to the Pirquet test has changed in about 50 per cent of the earlier positive cases.

In attempting to explain this change, the conditions required to produce a positive reaction must be stated. First, the organism must be infected with living tubercle bacilli, second, the organism must react to the infection, as every healthy organism does. But there are several states that produce anergy: acute infectious diseases, puberty, grave anemia, etc., in short, conditions producing asthenia. These conditions were absent in the nurses and other groups examined, as all those tested were healthy at the time of the investigation. There is, therefore, scarcely any reason to believe that 50 per cent of the persons gave a negative reaction because of the lack of necessary strength to react. On the contrary, everything seems to indicate that those tested were in the best condition to react, as will be shown later. Thus there is but one known possibility left, that is, the infection itself, the prime con-

dition for the reaction, is lacking. This seems to be reasonable, because tuberculous infection can rapidly or slowly kill or be killed by the organism. The latter fate has befallen the infection among the nurses who gave a negative reaction to the Pirquet test. They were infected in childhood and gave a positive reaction to the test, but the organism has little by little conquered the infection, and between the ages of 20 and 25 the infection has burned out, the positive reaction to the Pirquet test caused by the childhood infection has disappeared, and they are again virgin soil for a new infection, just as they were when they were new-born.

This is only a theory, but it agrees with the pathologic-anatomic researches. The late Dr. Jens Bugge of the Pathologic-Anatomic Institute of the University of Oslo has shown that there were no signs of living tubercle bacilli in about 30 per cent of the sections in which traces of tuberculosis were found.

The theory of a burned out infection and virginal soil for a new infection is mentioned in the second part of this paper.

TABLE 2—*Number of Nurses with Tuberculosis That Gave Positive Reactions and Number That Gave Negative Reactions to the Pirquet Test*

| | Positive | Negative |
|------|----------|----------|
| 1921 | 0 | 13 |
| 1925 | 2 | 17 |
| 1926 | 1 | 14 |
| 1927 | 0 | 4 |

NUMBER AND CLASSIFICATION OF TUBERCULOUS NURSES

The total number of cases of tuberculosis that have developed in the pupil nurses is fifty, but they have not been found in equal numbers among the groups that gave positive and negative Pirquet reactions. The distribution is shown in the table.

As far as the rest of the nurses who originally gave a negative reaction to the Pirquet test are concerned, only one of the 1924 class, two of the 1925 class and six of the 1926 class still gave negative reactions. I shall refer later to the group which started in January, 1927. But it can now be stated as certain that in the course of one or two years, the reactions of practically all of those who formerly gave a negative reaction to the Pirquet test have become positive, and that about 20 per cent of them have contracted a tuberculous infection. This seems to show that they were uninfected and presented a virgin soil when they began their hospital service, and that they soon contracted an infection.

If now the two groups are considered, the healthy nurses who gave a positive reaction as a result of an old infection, and the healthy nurses with a negative reaction who soon became infected, it is seen that fresh

tuberculous infection causes the greater number of cases of tuberculosis, an old infection seldom develops into the disease. In other words, the tuberculous infection generally shows its tendency at once either to conquer the organism or to be conquered by it and to establish immunity which is expressed by the Pirquet reaction.

Should this matter be considered with special regard to the Pirquet reaction, it would seem that a positive reaction in a healthy person shows immunity against tuberculosis. It would then seem natural to attempt to obtain a positive reaction without infecting the subject with virulent tubercle bacilli.

IMMUNITY TO TUBERCULOSIS

I have succeeded in obtaining a positive reaction to the Pirquet test by using the avirulent tubercle bacilli (Bacille-Billie-Calmette-Guerin). This was originally a tubercle bacillus, *typus bovinus*, of general pathogenicity which Professor Calmette¹ and his collaborators at the Pasteur Institute of Paris brought to nonpathogenicity without loss of other special peculiarities, especially the tuberculin-producing capacity. They did this by cultivation on a medium of potato-glycerin plus 5 per cent of bile through 230 passages in thirteen years.

The nonpathogenicity of this bacillus has been tested in every way by inoculations of all kinds into various animals. It is interesting to note that inoculation of huge doses into thousands of guinea-pigs and anthropoid apes has not caused the development of tuberculosis in any case. Of still greater importance is the fact that the animals thus inoculated with nonvirulent bacilli have acquired resistance against infection by virulent tubercle bacilli and are immune as long as this infection lasts.

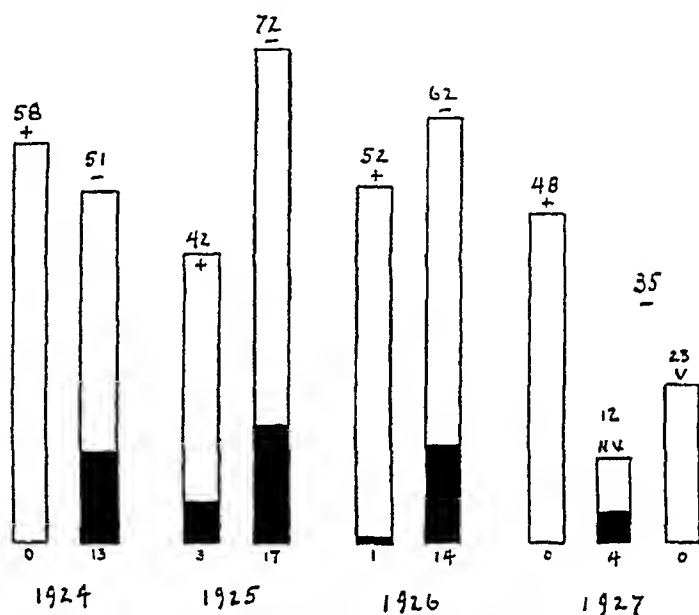
This is in agreement with Koch's theory of immunity to tuberculosis, namely, that as long as a person is infected with it, he cannot acquire a new infection.

In the fight against tuberculosis among cattle in France, this method has been used with much success. Professor Calmette has tried it on human beings and found it to be suitable for only those who were not already infected. Because of the widespread belief that every one has an infection earlier or later in childhood or youth, Professor Calmette selected for his tests young children most threatened with tuberculosis, namely, new-born children of mothers with open tuberculosis. In this group the mortality was extremely great. Statistics show that when a child remained with the mother the death rate during the first year was 125 per cent in France, excluding Paris, in other countries, it was as high as

¹ Calmette, A., et al. *Presse méd* **33** 825 (June 20) 1925, **34** 241, 1409, 1926. Calmette, A. *Presse méd* **34** 897 (July 17) 1926.

72 per cent With few exceptions these children are free from infection at birth Professor Calmette gave each child 1 centigram of a suspension of bacilli by mouth three times at intervals of three days, the first dose being given as soon after birth as possible, before infection from the mother To date, about 30,000 children have received this treatment in France and in her colonies, and it has not been reported that harm has resulted Among the 1,200 children closely observed and controlled for a year or more, the mortality from tuberculosis dropped to 1 per cent

Because the BCG bacilli are not harmful to children or animals and because the BCG bacillus infection seems to induce resistance or immunity to tuberculosis in children, I began to use it on nurses who gave a negative reaction to the Pirquet test and who were supposed to be in the same



Pupil nurses grouped according to von Pirquet reaction showing incidence of tuberculosis Numerals at the top of the columns indicate the number of nurses in each group, + indicates that the Pirquet test was positive, — that the Pirquet test was negative, *N* in column eight shows number not inoculated, *V*, in column nine, number inoculated with BCG bacilli Numerals at the bottoms columns indicate the number of cases of tuberculosis that developed in each group Numerals, 1924, 1925, 1926 and 1927, indicate the year each group of nurses began training

receptive state to tuberculous infection as new-born children Because the oral inoculation of the new-born is based on the great permeability of the intestines which soon disappears, subcutaneous inoculation was used The dose given was much less because of the increased effectiveness and concentration of the bacilli when given subcutaneously, and about a year ago the first inoculation with 0.2 milligram of BCG bacilli in physiologic sodium chloride was used on two persons

The first trial was made on a man, aged 33, (autotrial) to ascertain the effect of the inoculation if it were given by mistake to a person with a positive Pirquet reaction during a temporary negative phase due to some anergy-producing state. He gave a positive reaction to the test and was inoculated in the left arm. One hour later, there appeared "rubor, calor and dolor" about the site of inoculation and "functio laesa" of the arm. The symptoms continued for several days, then localized about the site of the inoculation, and after six days an abscess developed. The pus from it contained many tubercle bacilli. Attempts to treat the abscess by aspiration with the needle failed, and the surgical treatment was then begun and the abscess healed after nine weeks. Fever or symptoms of disease were not present during the entire period of the trial, which must be considered as a Koch's reaction, and showed that there was no risk in inoculating a person who gave a positive reaction to the Pirquet test.

The second trial was made on a boy, aged 4, who had repeatedly given negative reactions to the Pirquet test. The same dose and site were used for inoculation as in the foregoing case. Fever did not follow the injection, and the only untoward symptom was a little infiltration about the site of the inoculation, which suppurated two and a half months later, this suppuration continued for five months. At this point, the boy gave a positive reaction to the Pirquet test.

Because of the abscess formation in the cases reported, smaller doses, 0.03 mg., were given the nurses who gave a negative reaction to the Pirquet test. Some of these subjects developed a little infiltration, others did not have any reaction. Those who did not react were given another inoculation of 0.05 mg. a week later. Within four weeks after the second dose, there developed a small infiltration which was still present at the end of seven and one half months. All gave a positive reaction to the Pirquet test after six weeks. I consider 0.05 mg. the most suitable dosage, as this produced a local reaction, infiltration which signifies that the organism really has reacted to the inoculation. This method has been used in about forty cases.

The result of the inoculations has been, namely, all those who were inoculated gave a positive reaction to the Pirquet test after a sufficient length of time. The time between the inoculation and the appearance of the reaction has been from eleven days (a boy, aged 4, given a dose of 0.2 mg.) to eight weeks, averaging from about four to six weeks. About one half of those inoculated had an infiltration the size of a pea, of these, three suppurated, the suppuration was easily controlled. The others who were inoculated did not have a reaction, local or general, except that the Pirquet reaction became positive. The intensity of the reaction has varied from 1 or 2 sq. mm. along the scratch, to 10 mm. of rubor and infiltration. The meaning of this difference in reaction is not at this time apparent. The duration of the positive reaction to the Pirquet test and the allergy expressed by it is not known, in all cases that I have been able to follow it has been stable through the period of observation up to one year (in one case).

One group on which the tests were made I shall mention especially, that is, the group of nurses with a negative Pirquet reaction who started their hospital training in January, 1927. There were twenty-three nurses. They were informed of the earlier results of the research and were asked whether they wished to be inoculated with the Calmette bacilli. Twelve wished to be inoculated, and this was done as soon as possible after they entered the service. Before inoculation and during the first weeks following it, they were not allowed in the tuberculous wards, so as to protect them as much as possible against malignant tuberculous infection during the period immediately following vaccination. Eleven of them refused to be inoculated. The result was that up to the present time, four of the eleven with negative reactions to the Pirquet test who refused vaccination and who worked in the hospital among its tuberculous patients have a tuberculous disease, but of the twelve who were vaccinated and whose reaction to the Pirquet test in this way became positive, none has a tuberculous disease.

SUMMARY

Researches among nurses have shown that at the age of 20, the age at which tuberculosis shows the greatest frequency, about one half of those examined give a negative Pirquet reaction, among these, with few exceptions, the cases of tuberculosis occur. When nurses who gave a negative reaction to the Pirquet test were inoculated with Calmette's avirulent tubercle bacilli, the Pirquet reaction became positive. The preliminary experience with those inoculated seems to show that inoculation coincidentally produces some resistance and immunity to virulent tubercle bacilli. Time and further observation will prove or disprove this theory.

AGRANULOCYTIC ANGINA

REPORT OF A CASE

LAWRENCE K GUNDRUM, M D

LOS ANGELES

Agranulocytic angina was first reported by Schultz¹ in 1922. In June, 1927, Kastlin² reported two cases and reviewed forty-one previously reported. Since Kastlin's monograph, Linthicum³ has reported two cases and Finnegan⁴ one. Of the forty-seven cases reported (including the one given below), forty-three (91 per cent) terminated fatally. Thirty-seven (78 per cent) occurred in females, the majority of whom were past the age of 40. In only one case was there a history of a previous attack.

The disease is characterized by an acute onset with a temperature of from 101 F to 105 F, with great prostration, sore throat or mouth and severe headache. It is sometimes accompanied by chills, general muscle pains, vomiting, herpes, bleeding from the oral and vaginal mucosa and jaundice. A membrane is usually present either in the region of the tonsils or along the gingival margins. In the fatal cases, the external genitalia are often involved, which may progress to deep ulceration. Usually glandular involvement is not marked. The blood picture shows a marked reduction of the number of granular leukocytes. *Bacillus pyocyaneus* has been isolated in a number of cases, and in none of these has recovery taken place. In several cases the bone marrow was found to be cell poor and the spleen enlarged at autopsy. However, these observations are not constant.

REPORT OF A CASE

History—Mrs. K., aged 58, came under observation at 7 p. m., July 23, 1927. She complained of fever and sore throat. The family history was unimportant. The past history showed that there had always been a tendency to infections following any abrasions of the skin. For several years, she had had attacks of pain beginning in the right gluteal region and radiating down the back of the leg. On Feb. 1, 1927, she developed a sore throat. The pharynx, uvula and tonsils were covered with white patches. The uvula and tongue were swollen. A rash characterized by slightly raised red spots about the size of a dime covered the entire body. The rash did not become vesicular or pustular, but it caused great itching. This condition lasted for ten

1 Schultz, Werner. *Deutsche med. Wchnschr.* **48** 1495 (Nov. 3) 1922.

2 Kastlin, George J. *Agranulocytic Angina*, *Am. J. M. Sc.* **173** 799 (June) 1927.

3 Linthicum, Fred H. *Pyocyanic Stomatitis with Agranulocytic Leukopenia*, *Calif. & West. Med.* **27** 78 (June) 1927.

4 Finnegan, Frank P. *J. Missouri M. A.* **24** 258 (June) 1927.

weeks. A temperature of 100 F to 104 F was present throughout this period. It receded gradually. During the entire attack, frontal and occipital headache was present constantly. The patient was told that she had a heart murmur at this time. The pain in her right gluteal region increased, with local swelling and tenderness. The swelling was incised, and a large amount of pus was obtained. During the following twenty-eight days, her general health was good, and the patient gained 20 pounds (9.0 Kg), then suddenly she developed a similar rash, accompanied by anorexia and severe prostration. The next day the throat became sore. The entire pharynx was covered with a white membrane, the uvula was swollen and stiff, the "entire throat discharged pus." The temperature was 100 F to 104 F. She had severe headache and nausea, and frequency of micturition with burning. At the end of two weeks, all of the symptoms had disappeared except the painful micturition.

The present attack began on July 22, 1927, with a similar rash followed by sore throat. Essential points in the examination when the patient was first seen (July 23) were as follows: a few small rose colored herpetic areas on the wrists about the size of a dime. The tonsils were slightly enlarged and red. There was some swelling behind the right tonsil, there was not any evidence of fluctuation, neither exudate nor a membrane was present. The cervical glands were slightly enlarged and tender. The temperature was 103.2 F, and the pulse rate 90. Results of examination of the heart and lungs were negative. On July 24 and 25, the condition was unchanged, except that the patient complained of more severe pain on swallowing. On July 26, a small amount of thick tenacious mucopus was removed from the region of the right tonsil. During the day, the temperature dropped from 104.4 F to 101 F. There was great difficulty in swallowing.

Examination—A complete physical and neurologic examination by Dr. E. L. Armstrong showed that the heart and lungs were normal. A slight enlargement of the spleen was noted, otherwise the results of the examination were negative. On July 27, all symptoms increased. The throat became filled with stringy mucopus, and a few small grayish patches on the pharynx appeared to be easily removable without bleeding. The uvula was slightly swollen. The genitalia were not involved. There was no pathologic process in the heart, and a few crepitant rales were heard in the lungs. The temperature was 102 F to 104 F. On July 28, at 4 a. m., the heart became irregular and at 5 a. m., the patient became comatose, she died at 9 a. m.

Laboratory Examination—On July 25 an examination of the urine showed a small amount of albumin, a trace of sugar, a great deal of diacetic acid, fine granular and a few epithelial casts and pus cells.

On July 26, the blood examination revealed erythrocytes, 5,555,000, hemoglobin, 86 per cent, color index, 0.77, leukocytes, 660, lymphocytes, 82.5 per cent, polymorphonuclears, 16.0 per cent, and basophils, 1.5 per cent. The amount of non-protein nitrogen was 42 mg per hundred cubic centimeters of blood. The Wassermann test was negative. Culture and smears from the nose and throat showed abundant growth of mixed flora. Smears from the mouth were normal.

Tests for *Bacillus diphtheriae*, Vincent's bacillus and *B. pyocyaneus* were negative. Blood examination made at 9 a. m., July 27, revealed icterus index, 16.0 per cent, leukocytes, 340, lymphocytes, 92 per cent, polymorphonuclears, 8 per cent. Tests at 5 p. m. showed leukocytes, 280, lymphocytes, 94 per cent, and polymorphonuclears, 6 per cent. Changes had not occurred in the urine. Cultures from the nose and throat were negative for *Bacillus diphtheriae*, Vincent's bacillus and *B. pyocyaneus*. A blood culture was negative.

At 8 a. m., July 28, the leukocyte count was 310.

Treatment and Course—Treatment apparently did not have any effect on the condition. The first three days the throat was treated daily with 25 per cent silver nitrate and 10 per cent mercurochrome-220 soluble every three hours. During the last three days, a mouth wash of 70 per cent alcohol was used every three hours. A blood transfusion of 500 cc was given on July 27, a reaction did not occur.

Autopsy—Autopsy did not aid in the diagnosis. A mild, cloudy swelling of the viscera was present. The bone marrow was normal. A pure culture of *B. coli-communis* was obtained from blood of the heart and from the cervical lymph nodes, the organism was probably an agonal invader. Cultures from the throat after death showed the same flora as before.

COMMENT

The unusual features of this case were (1) the history of two previous attacks, (2) the extremely low white blood count (210 per hundred cubic centimeters of blood), and (3) the fact that all viscera and the bone marrow were essentially normal.

The number of cases recently reported make it probable that this condition has been overlooked in the past and is more common than would seem from the paucity of the reports. The diagnosis can be made certain only by the blood examination. A marked leukopenia with a relative increase of lymphocytes is always present. Other symptoms are variable. The only case in which treatment has been of any value is the one reported by Finnegan. He believes that the blood transfusion cured his patient. A 70 per cent alcohol gargle has been recommended on the theory that it is germicidal for *Bacillus pyocyaneus*.

This report is given with the hope that this malady may be recognized more frequently and that eventually a satisfactory treatment may be discovered.

1920 Wilshire Boulevard

STUDIES IN ASTHMA

II AN ANALYSIS OF TWO HUNDRED AND THIRTEEN CASES
IN WHICH THE PATIENTS WERE RELIEVED
FOR MORE THAN TWO YEARS *

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As I have recently suggested,¹ the causes of asthma are manifold and group themselves like the parts of a tree. The main trunk of the tree represents a fundamental basis which may be called the "asthmatic state" and explains why some persons have asthma and others do not. The roots of this tree represent the causes of the asthmatic state, but so far only one root—that of inheritance—can be recognized. Upward, the tree divides into two main branches—the extrinsic and the intrinsic. Both of these can be traced through numerous subdivisions. The extrinsic branch divides into pollen, animal danders, domestic and other dusts, foods and other substances, all of which are readily recognized. Twigs on these smaller branches represent, of course, the particular pollens, the different animals, the different dusts, etc. The main intrinsic branch is likewise subdivided into groups of causes, chiefly "bacterial" and "reflex," as outlined in recent papers.²

Such a conception as this tree represents merely a working basis, and the theory suggests a number of questions for consideration. When one speaks of "ragweed asthma" or "cat asthma," does one imply merely that the person has inherited or acquired a biologic hypersensitiveness to ragweed or to cats, and that the asthma which results from contact with ragweed or cats is a manifestation of this hypersensitiveness and that this alone can explain the entire situation? On the other hand, should it not be recognized that asthma is a characteristic symptom-complex, and that in spite of its manifold causes, its essential mechanism is the same in each case? Is it not reasonable perhaps to assume that the various substances which precipitate the attack in the patient are merely exciting causes and represent only the trigger mechanism which fires the attack but do not tell how or why the gun was loaded?

* From the Medical Services and Anaphylaxis Clinic of the Massachusetts General Hospital.

* The expenses of this investigation were met by an anonymous donation known as the "M G H Asthma Fund."

1 Rackemann, F M. Asthma, in Cecil, R L, and Kennedy, F. Textbook of Medicine, Philadelphia, W B Saunders Company, 1927, p 481.

2 Rackemann, F M. Studies in Asthma. 1. A Clinical Survey of 1,074 Patients with Asthma Followed for Two Years, J Lab & Clin Med 12:1185, 1927.

In other words, can asthma be regarded merely as an expression of a changed immunologic reaction to various foreign substances and should one not include the conception of a changed physiologic process which makes the new immunologic reaction possible? How else can one explain the fact that a small number of persons become hypersensitive to ragweed or to cats, when such an immense number of other people are exposed, apparently, to an equal extent, but never have trouble?

Many authors appear to assume that all asthma is of extrinsic origin and that if the exact cause cannot be identified, the difficulty lies in their own faulty technique. I maintain, however, that this point of view is unnecessary, and I hope to show that in certain cases extrinsic causes can be excluded, and that the exciting cause (the trigger mechanism), as well as the fundamental cause, lies within the patient's body.

To throw light on these various questions, a clinical study of asthma was undertaken on a pretentious scale. The gross results of this study have been published recently,² with a classification of the patients and a statement of total end-results obtained by a follow-up of 1,074 patients with asthma who were seen at the Massachusetts General Hospital and in private practice prior to Jan. 1, 1925, and who, therefore, have been followed for two years or more.

These results include the reports from 213 patients who maintain that they have been entirely free from asthma and without treatment for at least two years, and who are therefore designated as "cured," a word which is used for convenience, but always with skepticism.

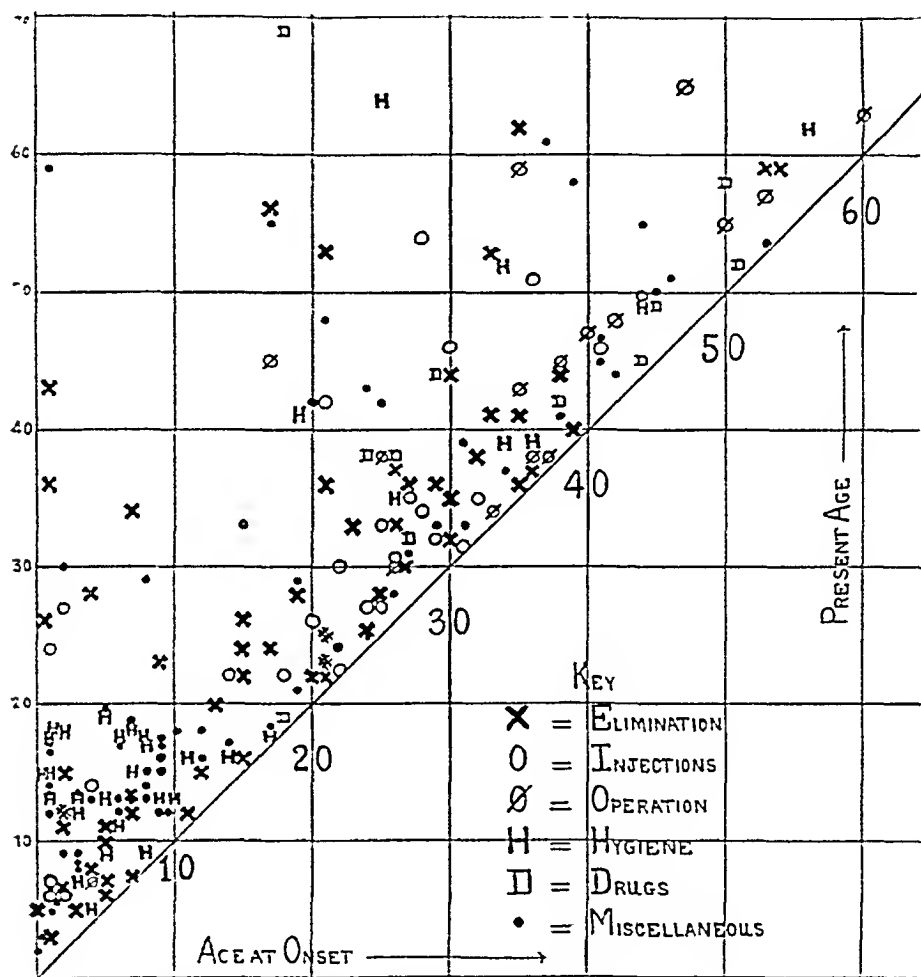
A further analysis of these 213 "cured" cases ought to throw light on the method of "cure" and consequently on the mechanism of asthma. It should show whether "cure" was accomplished simply by removal of the "trigger" mechanism, which was therefore only temporary, or whether it depended on a fundamental change in the physiologic and immunologic reactions. Further, it should suggest the general nature of the "asthmatic state" so far as the method of "cure" would rule in or out such possibilities as an anatomic nerve reflex between the nose and bronchi, some endocrine imbalance or perhaps an obscure chemical change.

Incidentally, it was anticipated that this particular study would demonstrate that the conception of a foreign protein excitant is not always necessary, and that it is proper to conceive that asthma has an exciting cause within the body, this cause is called "intrinsic."

With these thoughts in mind, the various groups of "cured" patients have been studied with several objects in view. First, to recall the classification and the clinical picture of the patients at the time of their first examination, over two years ago; second, to study the method of "cure"; third, to analyze critically the extent of "cure" and fourth, to note the incidence of foci of infection and other lesions in the "cured" cases, partly to rule out these lesions as factors in the mechanism of the asthma.

in the particular case and partly to determine to what extent "cure" can obtain in the face of these lesions

The accompanying chart shows the age at the time of "cure" of these patients plotted against the age at onset. The apparent method of "cure" is shown by the different symbols indicating elimination, operation and other factors as will be discussed. "Cures" fall into all age groups, but are particularly numerous among those who began to have asthma during childhood



Method of cure in two hundred and thirteen "cured" patients

The percentage relationship of the cases in which the patients were 'cured' to the total number of cases is shown in table 1, which gives the figures in each decade of onset. According to these figures, the change of "cure" apparently is not much greater when asthma begins in one decade than when it begins in another, except for the better prognosis among those with an onset during the first decade. Sixty-five per cent of all children with asthma were boys, and boys formed 73 per cent of the 'cured' children, so that boys have a greater chance of developing

asthma and also have a greater chance of recovery. In other terms, 30 per cent of 201 boys were "cured," while only 20 per cent of 112 girls were "cured." In the later decades, up to the sixth, the number of men and women was about the same, both in total numbers and in "cured" cases.

These figures fail to show any regular relationship between "cure" and age or between "cure" and sex, and suggest that since the occurrence of "cure" in this series is so evenly distributed, it is merely incidental.

The relation of "cure" to classification is more important. The methods of classification have been described in the first study,¹ and in that paper it was shown that 425, or 40 per cent of the 1,074 patients had extrinsic asthma, while 499 or 46 per cent had intrinsic asthma, the remainder being unclassified. The "cured" patients formed 25 per cent of the extrinsic group, 18 per cent of the intrinsic group and 10 per cent of the unclassified group.

TABLE 1—*Percentage Relationship of the "Cured" Cases to Total Cases*

| Decade of onset | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60+ | Total |
|---|-----|-------|-------|-------|-------|-------|-----|-------|
| "Cured" patients | 84 | 29 | 45 | 32 | 14 | 8 | 1 | 213 |
| Males "cured" | 61 | 13 | 19 | 13 | 7 | 2 | 0 | 115 |
| Percentage | 73% | 45% | 42% | 41% | 50% | 23% | 0% | 54% |
| Total patients | 313 | 166 | 202 | 183 | 129 | 59 | 22 | 1,074 |
| Total males | 201 | 75 | 82 | 87 | 73 | 36 | 14 | 568 |
| Percentage | 65% | 45% | 41% | 48% | 57% | 61% | 64% | 53% |
| Percentage of "cured" to total patients | 27% | 17% | 22% | 17% | 11% | 14% | 5% | 20% |

EXTRINSIC ASTHMA

In the extrinsic group, the "cured" cases occurred among patients with various subclassifications of the disease, as shown in table 2.

Simple (Uninfected) Pollen Asthma—In this group of seventy cases, there were thirteen patients who were "cured." These thirteen cases included ten adults, varying from 22 to 57 years of age, and three children. All had asthma which was limited to the pollen season and which was due to ragweed in seven cases, to grasses in three and to both ragweed and grasses in three others. The "cure" of patients with asthma was brought about in eight cases by treatment with ragweed which was combined with treatment with grass pollen in the three cases in which the patients were sensitive to grass. Every patient was treated during several successive seasons, usually four or five, but two patients, aged 43 and 23, were treated for only two years, however, they have not had asthma or hay-fever since the last treatment, which was given five and eight years ago, respectively. Apparently, the result is permanent. Four others report a complete relief from asthma, but do not mention hay-fever. Two of the eight patients treated, however, still have some

symptoms of hay-fever and give positive skin reactions to ragweed, so that they are not "cured"

In addition to the eight patients "cured" by injections, there were five "cured" by other means. One patient attributes his "cure" to a tonsillectomy, although two years previously he had had a series of injections of grass pollen with good results that year, while in four instances a definite cause for "cure" was not apparent. Two of these four patients had previously had several series of injections of pollen extract followed by some improvement. One of these patients, a man aged 22, who had had asthma all of his life, gave positive reactions to

TABLE 2—Classification of 213 "Cured" Cases Showing the Method of "Cure"

| Clinical Classification | Method of "Cure" | | | | | | Total "Cured" | Grand Total | Per centage "Cured" |
|--|------------------|-----------------|-------|-----------------|--------------|--------------------|---------------|-------------|---------------------|
| | Chimi- nation | Injec- tions | Drugs | Opera- tions | Hy- giene | Miscel- laneous | | | |
| Pollen asthma | 0 | 8 | 0 | 1 | 0 | 4 | 13 | 70 | 19 |
| Infected pollen asthma | 0 | 2 | 0 | 0 | 1 | 2 | 5 | 39 | 13 |
| Summer asthma, negative tests | 1 | 0 | 0 | 0 | 2 | 7 | 10 | 32 | 31 |
| Animal asthma | 16 | 3 | 0 | 0 | 1 | 2 | 22 | 60 | 37 |
| Infected animal asthma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 13 | 0 |
| Mixed and unidentified | 16 | 1 | 0 | 0 | 0 | 5 | 22 | 121 | 16 |
| Mixed and unidentified with negative tests | 16 | 0 | 0 | 0 | 1 | 1 | 18 | 37 | 40 |
| Extrinsic specials | 9 | 3 | 0 | 0 | 2 | 3 | 17 | 53 | 32 |
| Total extrinsic cases | 58 | 17 | 0 | 1 | 7 | 24 | 107 | 425 | 25 |
| Bacterial asthma | 1 | 6 | 5 | 2 | 3 | 8 | 25 | 202 | 12 |
| Bacterial asthma in children | 1 | 2 | 0 | 0 | 15 | 16 | 34 | 90 | 38 |
| Reflex asthma, not nose and throat | 0 | 1 | 0 | 4 | 7 | 6 | 18 | 66 | 27 |
| Reflex asthma, nose and throat only | 0 | 0 | 0 | 9 | 0 | 1 | 10 | 40 | 25 |
| Cardiac asthma | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 56 | 2 |
| Bronchitis and emphysema | 0 | 0 | 1 | 0 | 1 | 1 | 3 | 45 | 7 |
| Total intrinsic cases | 2 | 9 | 7 | 15 | 26 | 32 | 91 | 499 | 18 |
| Unclassified asthma | 2 | 0 | 4 | 0 | 0 | 9 | 15 | 150 | 10 |
| Grand total | 62 | 26 | 11 | 16 | 33 | 65 | 213 | 1,074 | 20 |

skin tests with ragweed injected intradermally. He was treated with ragweed extract and was greatly improved. After two years of supervision, he was lost track of, and on returning after an interim of five years without treatment, he gave negative reactions to pollens by scratch test. At this time, he was having attacks of asthma infrequently, and never severely, as before treatment. Although he was not treated for asthma, two years later this condition disappeared and he has not had a return of symptoms during the three years since then.

Lesions in the nose and throat were found in three of the thirteen patients, the tonsils being a focus of infection in two and the antrum in the third. One of the patients has been mentioned as being "cured" by operation, and the other two have become symptom-free in spite of the fact that they had not been treated for this condition, which suggests

that the focus as found was acute and self-limited instead of chronic and persistent, in any case, it had nothing to do with the symptoms

Infected Pollen Asthma—The fact that in this group of thirty-nine patients only five were "cured" illustrates the obstacle which secondary infection puts in the way of successful treatment. The five patients were all adults "cured" at or before the age of 40. Three were sensitive to ragweed, the fourth to grasses and the fifth to both. Three of the patients were treated with pollen extracts, two were "cured" by this alone, while the third was not completely relieved until her bad teeth were extracted. Of the two patients not treated with pollen extracts, one, a woman, aged 34, still has hay-fever, but she has not had asthma since resection of her nasal septum, three years ago. The other, a boy now 19 years of age, "outgrew" his trouble coincident with marked improvement in his general health at the age of 17, two years ago. He has lived in the same house all his life.

Summer Asthma with Negative Tests—Thirty-two patients were included in this group, ten of whom were "cured," ten were improved, ten remained in the same condition and two died. The diagnosis, unconfirmed by any tests, was based solely on the history of asthma limited to the summer months. In the whole group, only 10 per cent of the patients had a positive family history in contrast to the figure of 47 per cent for all extrinsic cases, curiously, this 10 per cent included only one of the ten "cured" patients.

Five of these ten "cured" patients were healthy adults, and five were children with asthma of only a few years' duration and limited entirely to the summer months.

The results of the physical examination were normal for all except one child who had a barrel-shaped chest, a roentgenogram showed increased shadows of the hilum. Three patients, one adult and two children, had a focus of infection in the tonsils, one was operated on with temporary relief and one without improvement.

The method of "cure" varied. Two of the children had their tonsils removed and also received hydriodic acid, which was given to two others together with a vaccine. Three adults also received iodides, with vaccine in one instance. These seven cases are described as miscellaneous because the method of "cure" was so uncertain. One of the children did not receive any treatment other than general directions for rest and a more regular dietary, and this "cure" by such improved hygiene was duplicated by one of the adults who likewise was not given any other treatment. The "cure" in one of the adults is credited to "elimination," because although the patient received iodides, one cannot be sure that the change in address was not important; perhaps her case should be listed in the unidentified group, in spite of the seasonal character of her attacks.

The duration of 'cure' in the ten patients has been from two to five years, in only two cases has it followed a change in environment, which might imply an escape from some offending pollen not included in the tests

Animal Asthma—Animal asthma of the simple type offers the best prognosis of any important subgroup. Of a total of sixty, twenty-two patients were "cured" and thirty-two were improved. In the group of twenty-two 'cured' patients, sensitiveness was manifested toward cats in eleven cases, toward horses in six, toward dogs in two, toward rabbits and guinea-pigs in one and toward a combination of two or more animals in the remaining two instances.

Specific treatment with the corresponding animal dander was attempted in seven adults, but the "cure" was attributed to the treatment in only two cases of horse asthma and in the one case of rabbit and guinea-pig asthma. The history of the latter patient has been published in detail.³ Toward the end of the treatment, each of these three patients could tolerate exposure to the particular animal without developing symptoms, and the three have been free from asthma for ten, four and two years, respectively. In sixteen other cases, the animal itself was eliminated, usually after treatment had failed, and this elimination was obviously the effective method of "cure." Three additional patients have become free from asthma without reference to the specific skin tests found. One of these was a school boy, aged 11, thin and sickly, who gave good reactions to test with cat hair, horse dander and feathers. When taken out of boarding school and left at home, he improved remarkably and has not had asthma during the past four years, he has gone back to school. His sensitiveness to animals was undoubtedly the exciting cause of the asthma, as shown by his prompt improvement at home, but his low vitality and chronic fatigue were perhaps of fundamental importance. Two men sensitive to horse hair do not know how they became symptom-free. One, who was formerly extremely sensitive, has not exposed himself to horses and now is free from asthma. The other is a hostler who is still at work and without symptoms. The last man gave a history of asthma during late August and September and frequently during the winter, but he did not react to skin tests with ragweed. The diagnosis was made by the slight test to horse dander in consideration of his occupation.

A focus of infection was found in the nose and throat in only one of the twenty-two asthmatic persons who were sensitive to animals. This patient had received several doses of cat hair extract and also had had her tonsils removed. Relief from asthma did not occur, however, until some time after this treatment, when the cat was eliminated. For the past two years she has not had any trouble.

3 Rackemann, F. M. *Asthma* M. Clin. North America 7:765, 1923.

Repetition of skin tests since the "cure" was established has been accomplished in only three of these patients, and in all of them the reaction was still positive, so that obviously the fact of "cure," in a literal sense, is open to grave question

While positive reactions to skin tests with animal dusts usually indicate a hypersensitiveness which is clinically important and thus lead to the relief from asthma by the elimination of the particular animal, these tests are occasionally misleading so far as the corresponding animal is of no clinical importance, whatever the cause of disease, the patient can be successfully treated without regard to the hypersensitiveness suggested. As will be discussed later, such tests may indicate past history rather than present illness

When infection occurred with animal asthma, not one of the thirteen patients in this series was "cured"

Extrinsic Mixed and Unidentified Cases with Positive Skin Reactions.—There is another considerable subgroup of extrinsic asthma. The twenty-two "cured" patients in this group represent 18 per cent of the total 121 patients with mixed and unidentified types of asthma who gave positive skin reactions

All of the patients reacted to several different extracts, most of which were extracts of different house dusts or house dusts in combination with other substances. Seven patients had hay-fever as well as asthma. Two gave a history of eczema during infancy, and one had hives after eating pickles or nuts or after drinking wine. Only seven had a positive family history

Of these twenty-two patients, sixteen were "cured" by a change of environment. Although ten of them had been treated by the extracts indicated, with good temporary results, an absolute freedom from symptoms was not acquired by any of them until, by change in residence, the patient escaped from some unidentified dust which was the exciting cause of the condition. These patients were all young adults who were "cured" at or before the age of 40, with the exception of one child, a boy, aged 12, who gave positive skin reactions to tests with house dusts and feathers, and who had symptoms only when visiting certain farm houses during his summer vacations. He was "cured" by following the advice to keep away from these old farm houses. Five years later, when he returned to the clinic in answer to a follow-up letter, he was tested again with house dusts, feathers, animal dusts and other substances, the results were negative

There were six other patients in this unidentified group whose method of "cure" is hard to define. One gave positive skin reactions to house dusts and to animals and was treated with these extracts with good results. She also had several bad teeth and some clouding of one antrum. Soon after the extraction of her teeth the antrum cleared up, and she became free from asthma. The second patient, a young man,

who gave strongly positive reactions to tests with mattress hair and house dusts, had round shoulders, a prominent abdomen a flat chest full of wheezy râles and a traumatic obstruction of his nose. He was advised to discard his hair mattress, to take regular exercise and regular rest, to have his nose straightened and to take benzyl benzoate. By one, or all of these methods of treatment, he has become free from asthma, although he still lives in the same house and in the same environment. In the third case, a child, aged 9 years, whose asthma began at the age of 2, and who gave positive skin reactions to tests with food and house dusts, the "cure" is attributed to an acute pulmonary infection, because he has been free from asthma for eight years following an attack of whooping cough which occurred several months after his first visit to the clinic. The fourth patient, a man, aged 42, gave positive skin reactions to tests with epidermal dusts and also house dusts, he also had a history of coryza after contact with dogs. Strange to say, his skin reactions, although positive to tests with cats and feathers, were negative to those with dog hair. This man was obese, and his chest was filled with mucous râles. He was advised to avoid animals and was given eight injections of a stock hemolytic streptococcus vaccine. About a year later, he returned with a cold, but he did not have asthma at that time nor during the two years intervening since then. One of the two remaining patients (both adults) was given injections of the pollen to which he reacted, without apparent benefit. He did not return for further treatment, but about a year later the asthma ceased for no apparent reason, and he has remained symptom-free for the intervening four years. The last patient also gave positive skin reactions to tests with house dusts, animals and feathers. He became free from symptoms, although this was not effected by a change in residence or by any particular avoidance of animals or feathers, he was given a series of stock vaccines, with good results, which may have helped in a general way.

A focus of infection in the sinuses was found in seven of the twenty-two patients, and two were operated on with improvement. A focus in the tonsils was found in three patients, but operation was advised in only one. There were two patients with abscessed teeth, and both were improved following extraction of the teeth.

In this group, then, change in environment resulted in complete relief from asthma in sixteen of the twenty-two cases. Treatment with house dust extracts or with other substances to which the patients reacted when skin tests were made, brought about "cure" in only one case. While the patients in three of the remaining five cases were treated, this treatment cannot be credited with the "cure" which could in each case be better explained in another way.

Extrinsic Mixed and Unidentified Cases with Negative Skin Reactions—An additional subgroup of thirty-seven patients includes eighteen

"cured" patients—a high proportion (The diagnosis in the other nineteen was made because the asthma also bore a definite relation to environment. Most of the patients are now improved, but a few others still have asthma because they have returned to the old surroundings.) These patients present the same clinical picture as those in the preceding group, except that their skin tests, by the intradermal method and often by the scratch method as well, were negative or so slightly positive that they were disregarded.

Only three patients had manifestations of hypersensitiveness other than asthma, two had hay-fever and one, urticaria. There was a positive family history in only six instances.

Of the eighteen "cured" patients, fourteen have been relieved of their asthma since they changed their residence, in spite of the fact that none of them gave the slightest reaction to skin tests with dusts. One boy, aged 15, was "cured" when the carpet in his room was changed, "on general principles", in spite of the negative reaction to skin tests, this boy was evidently hypersensitive to some foreign substance associated with that carpet. A baker, who associated his asthma definitely with the use of flour, but who gave entirely negative reactions to tests with wheat and other cereals, was improved by doses of extract and finally entirely relieved by changing his work so as to avoid wheat as a dust. In the remaining two cases, one patient was a girl, aged 13, whose asthma occurred only when she went to the family's summer home at the seashore. Advice in regard to cleaning and airing the house thoroughly, in addition to instructions for general hygiene (she was a thin, frail child) were followed by a "cure." In the other case, that of a child, aged 5, the "cure" cannot be definitely attributed to a change of environment, because this change followed soon after a series of injections of autogenous vaccine, which was already helping the patient. The extrinsic factor cannot be excluded, but neither can it be given full credit.

A focus of infection in the nose and throat was found in six of the eighteen patients. The sinuses were dull in four patients, and the tonsils were infected in three. Although operations were advised in several cases, they were never performed, except that in one case the patient had a nasal cauterization, which helped somewhat but did not effect the "cure." Abscessed teeth were not found.

Extrinsic Specials—The term applies to an interesting group of fifty-three patients known to be hypersensitive to some definite substance contained in the food or in the environmental dust. Industrial cases belong in this group. In spite of known etiology, only seventeen of these patients have been "cured." In eleven of them the cause of asthma was food, in six others, it was a dust.

The eleven cases in which the patients were sensitive to food include eight children, four of whom were poisoned by eggs, two by fish, one by wheat as bread and, finally, an infant, who was so sensitive to cow's milk that a few drops would cause swelling of the mouth, vomiting and urticaria, and yet whose reactions to skin tests, in spite of this high degree of sensitiveness, have never been large. One of the patients sensitive to egg was a boy, aged 16, who had been extremely sensitive to eggs and nuts since infancy. His case is of interest because he presented a picture of hypopituitarism, and because he has been immensely improved by the feeding of an extract of anterior pituitary. He has not had asthma since egg was eliminated from his food. In the group of patients sensitive to food are also three adults, two are women, aged 40 and 38, who became hypersensitive to foods at the ages of 19 and 33, respectively. Both have remained free from asthma, one for three and the other for seven years, since the offending foods (in one case celery, nuts and fish, in the other case, wheat and oats) were eliminated from their diet. The third was a student, aged 22, who since infancy had had asthma caused by eggs, and who was so sensitive that it was necessary for him to watch his diet with greatest care. He was "cured" by a series of twenty-seven hypodermic injections of increasing quantities of egg-white in watery solution.

The degree of "cure" in these food cases is not perfect. Although the student just referred to has not had any treatment for two years and now eats an egg for breakfast every day and is no longer troubled by cake and puddings, his test to egg-white is still positive. The two women, however, do not dare to change their diet, although one regards herself as "one of the wonders of the world" and the other has "forgotten I ever had asthma." One of the eight children still gives positive reactions to skin tests with eggs, the reaction to the scratch test being as large as it was seven years ago, nevertheless, the child eats eggs without difficulty. Two other children who were sensitive to eggs are eating eggs without trouble, but the two who were sensitive to fish still hesitate to indulge in this food, although they are free from asthma. The child who was sensitive to milk is now drinking 24 ounces of cow's milk each day. The boy who was sensitive to wheat has recovered from his asthma after avoiding bread for a year and a half, the boy with pituitary dysfunction also eats every kind of food and is well.

From this it appears that positive reactions to skin tests can occur without any relation to the symptoms or lack of symptoms. On the other hand, the positive tests in these cases agree closely with the symptoms observed during infancy and childhood, consequently, it is obvious that they serve merely as a record of past experience and are without bearing on the present condition. This is entirely in accord with the

observations of Mackenzie⁴ on bacterial hypersensitiveness as well as with the well known dependence of a positive tuberculin reaction found in adult life on a primary infection in childhood

The six cases in which the patients were sensitive to dust include two children and two adults who have not had asthma since they discarded their feather pillows. The fifth case is that of a grocer who was sensitive to hops and malt and who has been 'cured' by injections of malt extract. He is still at work in the same place. Finally, a housewife aged 32 has not had asthma since a series of treatments with orris power extract, to which she gave good skin reactions.

Comment on Extrinsic Asthma—The results as outlined bring out clearly that in most of these cases "cure" has been accomplished by removal or treatment of the trigger mechanism which fired the attack. Evidence concerning the permanency of the results is conflicting. While certain patients can return to the old environment or the old diet after a lapse of time and remain free from asthma, an equal or greater number remain hypersensitive, and symptoms return with repeated exposure.

In this last group it is obvious that the "cure" is merely temporary and that, although the trigger may have been disconnected for a time, the gun remains loaded. In the other group, however, there is evidence not only that the trigger mechanism has been removed, but that the load in the gun has been modified.

What relation do these cases bear to the young patients who have 'outgrown' their asthma? Does the material suggest any factors which may be common to all with a permanent "cure"? This subject will be discussed at the end of the paper.

INTRINSIC ASTHMA

Intrinsic asthma is more difficult to analyze. Indeed, the existence of such a type has been ignored by those authors who imply that every case of asthma depends on a hypersensitiveness of the patient to some foreign substance which may be unidentified either because the variety of test substances is not sufficiently extensive or because the technic is not sufficiently perfected. Such an attitude is not without reason.

The variety of test substances has been increased by the attention called to house dust by Cooke⁵ and to various fungi and molds by Van Leeuwen⁶ and physicians in every large clinic are constantly identi-

⁴ MacKenzie G. M. and Hangar H. M. Jr. A Study of Hypersensitiveness to Derivatives of Hemolytic and Non-Hemolytic Streptococcus. *Proc. Soc. Exper. Biol. & Med.* **21**:542, 1924.

⁵ Cooke Robert A. New Etiologic Factors in Bronchial Asthma. *J. Immunol.* **7**:147, 1922.

⁶ Van Leeuwen Storm, Bien Z. and Varekamp H. Neuere Erfahrungen über Diagnose und Therapie von Ueberempfindlichkeitskrankheiten (allergische Krankheiten). *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **37**:77, 1923.

fying various dusts met with in industries as materials to which the persons exposed will develop hypersensitiveness and symptoms. The large number of pollens which Duke⁷ and Rowe⁸ have identified as causes of hay-fever is being extended by many other workers. This improved technic has made it possible to show that certain patients formerly classed as having intrinsic or an unidentified type of asthma have extrinsic asthma and are hypersensitive to a previously unrecognized cause.

In addition to this improved technic there are other reasons for considering an extrinsic cause in many persons who give negative reactions to skin tests. Chief among these is the fact of relief from symptoms when the patient moves from one environment to another although reactions to skin tests with a wide variety of substances are entirely negative. This in turn suggests that a patient may have a clinical hypersensitiveness, confirmed by relief from symptoms when the cause is withdrawn, without giving positive reactions to skin tests. Such a conception would be of the utmost importance, but so far it cannot be proved. On the other hand I believe, as outlined in a previous article - that the clinical analysis of a certain number of patients leads to the logical conclusion that the cause of asthma in them must be intrinsic rather than extrinsic.

In the following discussion of the cases in the intrinsic group a few patients with positive reactions to skin tests have been included, but as will be seen a study of the history and environment has failed to show any relation between the symptoms and the particular substance with which the test was made. In this connection, it has already been pointed out in discussing food asthma that positive reactions to skin tests may represent past history rather than present illness.

The division of patients with intrinsic asthma into subgroups is difficult. It is easy to conceive of asthma dependent on infections of the larger bronchi and to designate these patients as having "bacterial asthma." It is easy to distinguish a second large group in which the cause is in the body but outside of the bronchopulmonary tree and to assume that asthma is a reflex effect of some stimulus arising from this extrabronchial source. Both these conceptions serve simply as working hypotheses and are without a basis of experimental proof. In spite of this, the classification is useful because typical cases in the bacterial and in the reflex groups can be recognized clinically, and it is important to study them further in order to determine whether a total disregard of extrinsic factors is justified by the clinical evidence at hand. When, however a

7 Duke, W. W. *Asthma Hay-Fever, Urticaria and Allied Manifestations of Allergy*, St. Louis: C. V. Mosby Company, 1925.

8 Rowe, A. H. *Pollen Counts in the East Bay Region with Studies on the Morphology of Pollen*. Read before the American Society for the Study of Asthma at Washington, D. C., May 16, 1927, to be published.

patient appears to have a bacterial asthma and at the same time is found to improve after the removal of a focus of infection, his classification becomes difficult and unsatisfactory

The group of bacterial asthma is the most important and characteristic of intrinsic asthma. For convenience, the fifty-nine "cured" patients have been separated into twenty-five adults and thirty-four children (table 2)

The typical patient has had asthma since an early age. This asthma usually began after an acute infection of the respiratory tract and has occurred in well defined attacks since the onset, each lasting from one to four weeks in the fall, winter and spring, but rarely in summer. These attacks occur without change in environment or occupation and often begin with "a cold." They occur at first only in the fall and spring, but later become more frequent, so that the interval between may be shortened to one or two weeks. Nevertheless, the interval exists, and in it the patient is free from cough and asthma and is essentially well in the same environment while leading his regular life. The interval is important, particularly when the conditions are the same, because it argues against any constant extrinsic factor. It is true that patients with typical extrinsic asthma have intervals between their attacks, but analysis will show that these experiences are always directly associated with the particular exciting cause. Reactions to skin tests in the group, as a rule, are negative to the common dust substances by the intradermal method.

Among the twenty-five "cured" adults the onset of asthma was, for the most part, between the ages of 20 and 40, though one patient, aged 26, developed it at the age of 8 and six others during their teens, five of whom were not 20 at the time of examination.

A story of an acute infection of the respiratory tract immediately preceding the original attack of asthma was obtained in only ten patients. Two other cases are of particular interest and suggest the possibility that chronic as well as recurrent infection may lead to asthma. One patient, a girl aged 20, had had several attacks of pneumonia during childhood and had had a running ear since the last attack twelve years ago. Asthma began at the age of 19, in November, after she had had a persistent cold, during the preceding winter she had had a cough. When examined at the age of 20, she was thin and pale. Coarse musical râles were found at the bases of the lung, but the apexes were clear. She recovered from her asthma at the age of 21, following tonsillectomy, five years later, at the time this article was written, she stated that she has one or two bad colds each winter, but that she has not had asthma.

The second patient, a girl, aged 26, weighing 97 pounds (44 Kg.), had had osteomyelitis of the femur since the age of 9. She had her first attack of asthma at the age of 24, following a cold in October. The

second attack occurred the next year, in November, and the third the following October, just before she was examined in the clinic. The culture of sputum showed a hemolytic streptococcus in predominance, and a vaccine of this organism was given that winter (1923). She has not had asthma since then.

The extent of "cure" is shown by the fact that in eleven cases five years have elapsed since the last attack of asthma, in five cases, four years, in five cases, three years, and in three cases, two years, and only five of the twenty-four patients mention the presence of colds in their follow-up letters.

The reactions to skin tests were positive in four patients, but were not of any clinical importance.

The method of "cure" is almost impossible to identify because these were all difficult cases, and many methods of treatment were applied. Vaccines were used in eight of the twenty-five patients and were apparently responsible for the "cure" in six. Drugs are given the credit in five patients (Potassium iodide in two, benzyl benzoate in one, emetine hydrochloride, subcutaneously, in one and a patent medicine in another). Elimination has brought freedom from symptoms in one, and a change in residence has completed the "cure" started by potassium iodide. The remaining "cures" in thirteen patients cannot be explained. For example, A man, aged 44, who had had asthma in typical attacks since he had had influenza in 1918, and who had a barrel-shaped chest and thick yellow sputum, "has never been bothered with asthma" since gastro-enterostomy for ulcer at the age of 48, three years ago.

A woman, aged 34, whose asthma began with a cold in May, a few months previous to her first examination, came to the hospital only once and did not receive treatment, however, she has not had asthma since a severe attack of influenza at the age of 36, nine years ago.

A thin nervous business man aged 48, who had had two attacks of asthma each year since the age of 21, was tested in a routine manner by the intradermal method and has not had asthma since that time seven years ago. Incidentally, the reactions to these tests were entirely negative, and his bad teeth have not been extracted.

A Jewish attorney, aged 39, who had had attacks of asthma following colds since the age of 34, has been entirely well since the correction of his constipation and the institution of daily exercise. His "cure" is ascribed to this improved hygiene.

In addition to the twenty-five adults, there were thirty-four "cured" children with 'bacterial asthma,' twenty-five boys and nine girls. The age of onset was under 5 years in eighteen, and between 5 and 10 in sixteen. This onset occurred immediately after colds or bronchitis in sixteen instances, in seven of which the preceding illness was sudden and severe (pneumonia in three, whooping cough in one and a bad cold

in three others) Another patient dates the onset from tonsillectomy at the age of 3 years

The physical condition of these children at the time of examination varied Such notes as "undernourished," "pale and thin" and "poorly developed" appear in the records of fifteen, but a barrel-shaped chest with emphysematous lungs was noted only once—in a boy, aged 12, who had had attacks of asthma which occurred every few weeks throughout the year since the age of 7

Diseased tonsils had already been removed in fifteen children, and three others showed infected tonsils at the time of examination A tonsillectomy was performed in one case

Evidence of sinusitis, with dulness of the antrums on transillumination or on examination by the roentgen ray, was found in five patients, all in their early teens, but drainage was not advised or attempted, the apparent method of "cure" was improving of the hygiene, although one boy, aged 13, was given a vaccine made from the staphylococcus found in his nose This boy is now a mile runner on a university track team

Eczema was mentioned in the past or present history of five of these children, one of whom gave a good reaction to tests with several cereals, including buckwheat, wheat and oats Two other children had had urticaria, one of them after eating strawberries

Skin tests, by the scratch method, using the common food and dust substances, were made on all but four of these "cured" children In addition to the child sensitive to cereals, three others gave positive reactions to skin tests, one to wheat, one to feathers and one to animals—the last child, however, was never exposed to animals, and the method of his "cure" cannot be defined, although he has been under the constant supervision of an excellent practitioner

The family history of thirteen children was positive, including four children with other allergy

The permanency of "cure" in these children can only be surmised Suffice it to say that seven have been free from asthma for five years or more, seven for four years, six for three years and fourteen for two years It is interesting that of the seven children free for five years, the method of "cure" in four consisted solely of measures to improve the general condition and hygiene None of these children had had any treatment by injections of vaccine or other substances, and reactions to skin tests were negative in all except in the case of the child with eczema who was sensitive to cereals, previously mentioned Curiously enough, this particular group of seven children includes five of the other seven children with either eczema or urticaria

In the entire group of thirty-four children, fifteen were "cured" by "general hygiene" without other measures and particularly without atten-

tion to foreign proteins. None of the fifteen had changed his address before the "cure" took place. Ten of the fifteen were undernourished, weak children, and the other five had bad habits of diet, rest and exercise.

In one case, the mother writes that she has discovered that asthma was due to eggs and apples, and that since her son has omitted them from his diet, he has not had any further trouble. This relation to certain foods was noted before the examination and tests with active extracts were made on two different occasions, but the results were always negative. Incidentally, the boy was given four doses of a stock vaccine and had his tonsils removed, after which he was much improved. His "cure," however, did not begin until about four years after the time of observation. The relation to eggs and apples was evidently not extremely close, but the data in table 2 show the "cure" by elimination.

Two children were "cured" by vaccine, stock and autogenous, respectively. While it appears that this treatment was important, a comparison with other cases, particularly in the hygiene group, clearly shows the fallacy of claiming too much for any method.

Finally, there are sixteen children whose "cure" cannot be attributed to any one particular method. For example, a child, aged 10, whose father was asthmatic, had had eczema as an infant and attacks of bronchitis at the age of 4. In spite of tonsillectomy at the age of 6, attacks of bronchitis recurred but asthma did not develop until he was 9, when the attacks were rather continuous from December to June. Reactions to skin tests, by both scratch and intradermal methods, were negative. He did not receive any treatment. The father writes that the attacks diminished in frequency and severity until they ceased at the age of 12. The boy is now 17 years of age.

Comment on Bacterial Asthma—The analysis of the cases of these patients with bacterial asthma who have been "cured" leads to a number of observations.

Bacterial asthma as a diagnosis is adequate, since the theory of recurrent infections of the respiratory tract as a cause of asthma fits the clinical picture better than any other conception which can be considered at present. The clinical history presented by most of these patients is sufficient to rule out the causative factors dependent on hypersensitiveness to a foreign protein.

The method of "cure" does not suggest any underlying mechanism which is common to a majority of these patients, but it emphasizes two important points. 1. General advice based on a common sense effort to improve the general bodily condition—referred to here as "hygiene"—is of great importance especially in children and makes many of these patients amenable to treatment by any physician and without special equipment. 2. The tendency of children to outgrow their susceptibility to infections of the respiratory tract is definite.

Reflex Asthma—The term reflex asthma indicates that clinically the cause of the asthma is based on a focus of infection in the body or on the faulty function of one or another organ. Table 2 indicates that in a total of 106, twenty-eight patients were "cured." These twenty-eight have been divided into those whose asthma was definitely attributed to a focus of infection in the nose and throat and those whose asthma was not attributed to this cause. The twenty-eight cases include eight children and twenty adults, both age groups including some patients with pathologic changes in the nose and throat.

Eighteen patients were "cured" of asthma which was designated as reflex from some source other than from the nose and throat. Six of these were children, all of whom were in poor general condition. In four of them asthma had been constantly present for from one to three years before examination, while in the two others, it had occurred in fairly definite attacks which were worse during the winter. The last two are, of course, analogous to the cases of bacterial asthma in children already mentioned, but they were originally placed in this reflex group because the immediate results of improving the general bodily hygiene, with directions for regulation of diet, rest and exercise were so striking. "Hygiene" accounts for the "cure" in all six patients, although three are listed as miscellaneous "cures" because one child had had vaccine treatment, another dates his "cure" from an attack of bronchopneumonia seven years ago, as since then his general condition has improved to a remarkable degree, and a third child, aged 11, not relieved by tonsillectomy at the time of examination, has not had asthma since an appendectomy five years ago, two years after his first visit to the clinic. Possibly, too, his slightly positive skin test to potato may have been important.

Only two of these children had a positive family history.

A focus of infection was found in three children—two tonsils and one sinus—but as appropriate treatment did not help them, these foci were disregarded.

The twelve adults varied in age from 16 to 62, and asthma was not developed before the age of 25, except in the two younger patients. The histories of these patients were atypical, as none of them told of clear-cut attacks characteristic of bacterial asthma. Reactions to skin tests were negative in all, two had changed their address, without causing any change in symptoms.

"Hygiene" was the method of "cure" in four of these adults who were advised to drink less tea, to eat more lunch, to lie down at noon-time and to eat foods containing less carbohydrates and fats, respectively.

Operative treatment accounts for four more, a man, aged 45, and another, aged 55, have not had asthma since the removal of bad teeth, a woman, now 45, has been free from asthma for seven years, since her

gallstones were removed when she was 38 years old and finally, a man, aged 62, who had a cholecystectomy has not had asthma since the operation was performed two years ago

In four patients, the method of "cure" is unidentified, chiefly because various methods of treatment, including a change in residence, were employed in each case. In them the designation of 'reflex' calls attention to other conditions present. One had a positive Wassermann reaction, and, as antisyphilitic treatment seemed at first to prevent asthma, syphilis was considered a reflex cause. A careful comparison between the changes in the Wassermann reaction resulting from treatment and the changes in asthma did not show any constant relation between the two, and at the present time, although the patient is free from asthma, the Wassermann reaction is still strongly positive. At various times she has also been given vaccines and she has had her teeth extracted. Another woman developed asthma during her first pregnancy, and had it again during the second, but she has not had asthma during the six following years. A laborer, aged 40, did not have any evident cause for asthma except bad teeth. He is now "cured," perhaps because his teeth have been removed.

Finally, a woman, aged 38, who had repeated attacks of asthma, each definitely connected with infections and relieved temporarily and in succession by appendectomy, by influenza during pregnancy and by removal of teeth and tonsils, has not had asthma since the administration of an autogenous vaccine three years ago.

The ten cases with a reflex cause in the nose and throat include those of two children. A girl, aged 12, who had asthma since an attack of influenza at the age of 9, had numerous polypi, dulness of the sinuses and badly infected tonsils. The polypi and tonsils were removed shortly after examination, with considerable improvement (six years ago), but her 'cure' dates from "about three years ago," and as she gives a new address the well marked lesions were perhaps unimportant, and the original diagnosis of reflex asthma should more properly have been extrinsic asthma. Another child was, however, definitely "cured" by tonsillectomy, and two adults have remained free from asthma for four and five years since tonsillectomy.

The other six adults had nasal polypi and degrees of sinusitis, and in every one of these cases the "cure" dated from operative treatment seven, five, four, three, three, and two years ago, respectively.

Reaction to skin tests by the patients in these reflex cases were always negative.

Cardiac Asthma and Chronic Bronchitis with Emphysema—The heading indicates that the asthma is associated with changes in the circulation or in the lungs which are organic, well recognized and permanent.

The 101 patients were elderly people, with the exception of seven young adults (now all in the forties) each of whom had a characteristic barrel-shaped chest, with clubbed fingers and chronic cyanosis

While one of the patients with heart disease and three of the patients with emphysema have been relieved of their asthma, the word "cure" cannot be used even in the loose sense in which it has been employed in this paper. A woman, aged 65, with severe asthma since the age of 17, which was not affected by residence in California, Maine or Carolina, was given potassium iodide when first seen in 1921, since then she has had but a single attack of asthma (in 1925). She has, however, recently developed symptoms of decompensation and of angina pectoris.

Two of the patients with emphysema were women aged 53 and 61, both had hypertension and both have been free from asthma for two and five years, respectively, since taking potassium iodide. The other patient, a Jewish tailor, aged 42, had a history of wheezing for twenty years, he had a slightly barrel-shaped chest. After coming to the hospital he became comfortable, and he has not had asthma during the intervening three years. His symptoms were obviously exaggerated as was the original estimate of his emphysema.

UNCLASSIFIED ASTHMA

Unclassified asthma is self-explanatory. Only 10 per cent of the 150 patients were "cured", these fifteen include thirteen adults and two children. Most of them were "cured" in some unidentified or miscellaneous manner. Drugs, however, were clearly responsible in four cases, iodide in two, acetylsalicylic acid in one and asphenamine in an interesting case, in which asthma was due to a gumma of the larynx. Two patients were "nervous". One an apprehensive French maid, who had asthma, both in the city and in the country, has not had asthma since going home to France, three years ago, although she returned to the same family and to the same house in the United States one year later. The other girl was a temperamental Italian who went to Italy four years ago, and who has been well since then. Her case is classed as miscellaneous and not extrinsic, because her asthma was of only five weeks' duration and cleared up to a considerable degree after treatment with iodide and vaccines, this was two years before her departure for Italy.

The cases of nine other patients remain unclassified, chiefly because the method of "cure" was bizarre, consisting of the use of electricity or an unknown "patent medicine" or simply of examination and skin tests without any definite treatment, yet all of the patients had a definite history of asthma. A few other cases are so complex that any satisfactory analysis of the histories and manifold methods of treatment is hardly worth while.

COMMENT

In the foregoing discussion of "cures" among individual patients and groups of patients, it is evident that the study as a whole is hardly susceptible of accurate analysis. On the other hand, the study of certain patients is based on objective observations which are accurate. In some of them, the method of relief can be identified, and although its mechanism is unknown, the word "cure" can be applied to the end-results with some confidence.

Table 2 not only represents the methods of "cure" in the various subgroups of cases, but also shows the relative importance of all these various methods in all cases. Thus in the extrinsic group, the elimination of some external factor is the important method, although in a few cases, treatment of the patient with an extract of the corresponding substance has been effective. "Cures" by hygiene and by miscellaneous methods are particularly numerous in the intrinsic group in which specific methods have yielded disappointing results, but it is impossible to define, with any accuracy, the mechanism by which this "cure" was brought about.

In reviewing the work it is important to determine the number of cases in which the method of "cure" is known and in which a true cure can be claimed. Such a study applied to this particular series is handicapped by the fact that only in a few cases of the intrinsic group as a whole were the skin tests repeated after the "cure" was established. The fact, however, that in these few the reactions to the retests were always positive makes the thought of time cure in the group doubtful.

At the same time, attention is called again to the children with asthma caused by sensitiveness to eggs who later were able to eat eggs in spite of the fact that their reaction to skin tests with egg-white is still positive. This suggests the thought that other positive reactions to skin tests relate to past history rather than to the present illness. Such an idea must modify the definition of a "cure" and justify the belief in a true cure even in the presence of persistently positive skin reactions.

Many of the patients have been "cured" by a change to a new environment, which has allowed them to escape from the cause of the asthma, in these cases also it is difficult to tell whether the result is permanent. Although several years of complete freedom from asthma have elapsed in a few instances, in other patients not "cured," whose cases are therefore not included in this paper, it was found that with a return to the old environment asthma recurred. In contradiction to the idea that such a gloomy outlook applies to all such cases is the story not uncommonly given that patients "used to be" sensitive to a cat, to feathers or to some particular dust, but find that now such an intolerance does not exist. It is unfortunate that more of the "cured" patients have not returned to the environment which caused their trouble so as to provide the data necessary to test their "cure."

The intrinsic group is even more difficult of analysis. It appears that vaccines cause a "cure" in some cases and that potassium iodide will relieve a patient with bronchitis markedly and perhaps permanently. On the other hand, both vaccines and iodides have been given to countless other patients without such results.

The operative treatment of patients with lesions in the nose and throat, the removal of bad teeth and other procedures are additional measures which will "cure" some patients, but in the vast majority of cases the effect is only temporary. A detailed study of the relation of the nose and throat to asthma is in preparation.

Throughout this paper, "cure" by "hygiene" is frequently mentioned. This shows that the principles of general medical care with attention to the patient as a whole are an important part of the management. When such simple measures as the relief of constipation, the readjustment of diet (without any attempt to omit or add a particular food) and the institution of good habits of rest and exercise can bring such excellent results in the proper cases, it is apparent that any physician with experience and common sense can do a great deal for asthmatic patients without the use of complicated apparatus or the making of tests which are often so hard to interpret.

"Cures" by "hygiene" are especially important in children. The chart shows the general distribution of "H's" but also a concentration of "H's" among those in whom asthma began at an early age and who are still children. Hygiene presumably does little more than allow nature to cure the disease, and then the child is said to have "outgrown" his asthma. This subject is so important that the end-results in all those who developed asthma at an early age have been tabulated.

Table 3 shows the results in the entire series without regard to the type of asthma or the method of treatment. There are 351 patients in whom asthma began before the age of 12. Of these, 288 are still under 20 years of age, while 123 are over 20. Patients who are "cured" and "greatly improved" (a designation which includes several patients who have been free from asthma for a year, but who are not yet eligible for the "cured" group) form 66 per cent of the 228 patients who are under 20 years of age, while good results among those now past 20 occur in only 38 per cent of the 123 cases.

Of more importance than the present age, however, is the age at which these children applied for treatment (table 3). Figures show that of the patients whose cases were studied before the age of 12, 33 per cent are "cured" and another 32 per cent are "greatly improved," a total of 65 per cent, whereas if study was postponed until the patients were older, the figures are reduced to 20 and 28 per cent, or a total of 48 per cent. The age of the patients when their cases are first studied, however, is roughly parallel to the exact age of onset, since 110 (61 per cent)

of the patients seen before the age of 12, developed asthma before the age of 5, while of those seen after 12, the age of the onset of the disease is a little later since the attacks began in only 88 (48 per cent) before the age of 5

These figures bring out the marked tendency of patients to outgrow asthma when it begins in infancy, they also show that the prognosis is better when the onset is earlier. As the highest figure is only 66 per cent it is evident that an attitude which is too complacent is dangerous, and that in spite of the favorable outlook all reasonable efforts to control the condition must be made in every case.

Is asthma which is "outgrown" different from asthma which is "cured" by hygiene and what factors have these cases in common with

TABLE 3—*Asthmatic Patients with an Onset Before 12 Years of Age*

| End Results | A Present Status According to Present Age | | | | | |
|------------------|---|----------|---------------|----------|--------|----------|
| | Under 20 Years | | Over 20 Years | | Total | |
| | Number | Per Cent | Number | Per Cent | Number | Per Cent |
| 'Cured' | 80 | 35 | 11 | 9 | 91 | 26 |
| Greatly improved | 70 | 31 | 36 | 29 | 106 | 30 |
| Improved | 54 | 24 | 41 | 33 | 95 | 27 |
| Same or worse | 19 | 8 | 22 | 18 | 41 | 12 |
| Dead | 5 | 2 | 13 | 11 | 18 | 5 |
| Total | 228 | 100 | 123 | 100 | 351 | 100 |

| End Results | B Present Status According to Age When First Studied | | | | | |
|------------------|--|----------|-----------------------------|----------|--------|----------|
| | Studied Before 12 Years | | Not Studied Before 12 Years | | Total | |
| | Number | Per Cent | Number | Per Cent | Number | Per Cent |
| 'Cured' | 55 | 34 | 36 | 29 | 91 | 26 |
| Greatly improved | 54 | 32 | 52 | 28 | 106 | 30 |
| Improved | 39 | 23 | 56 | 31 | 95 | 27 |
| Same or worse | 17 | | 24 | | 41 | |
| Dead | 3 | 12 | 15 | 21 | 18 | 17 |
| Total | 168 | 100 | 183 | 100 | 351 | 100 |

the occasional true cures in adults? Such thoughts as that of the changes at puberty or of the influence of endocrine glands are suggested, but there is no evidence to substantiate any one of them. In any case, it is evident that the chief mechanism of asthma is immunologic rather than physiologic or anatomic, but what controls and changes this immunologic reaction remains unknown.

CONCLUSIONS

The foregoing study is based on an analysis of 213 cases in which the patients have been relieved of their asthma for over two years. These 213 patients are merely a part of the total of 1,074 patients on whom the end-results are known, as previously reported.

The most common method of "cure" is by the elimination of or the escape from the particular external substance to which the patient is hypersensitive and which as the exciting cause (the trigger mechanism)

starts the asthmatic attack. In certain cases, especially in children, the removal of this trigger mechanism can result in a permanent cure, but in most of the cases, the extent of "cure" in asthma cannot be determined.

Clinical "cure," including absence of symptoms even in the presence of the supposedly offending substance, can exist in spite of the fact that reactions to skin tests are still positive, consequently, the thought that positive reactions may represent past history rather than present illness is presented.

Apparent "cures" following changes in environment may be permanent in some cases.

The removal of foci of infection leads to clinical "cure" in a few cases, although similar procedures do not help other patients who may later be "cured" by other means.

Faulty hygiene, often the result of asthma, may apparently be associated with the cause of asthma in a considerable number of cases, so that treatment based on the principles of common sense medicine is always important, especially as children tend to outgrow asthma, and this tendency can be assisted by good management begun as early as possible.

The evidence at hand fails to suggest any definite explanation of the asthmatic state, except that the basis is immunologic rather than physiologic or anatomic.

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EXPERIMENTAL ANEMIA PRODUCED BY CLOSTRIDIUM WELCHII

CHEMICAL ANALYSIS OF THE BLOOD *

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In a preceding paper,¹ the general problem of the significance of the anaerobic intestinal bacteria in relation to human disease was presented, and experimental studies of these microbes, more especially of those belonging to the species *Clostridium welchii*, were described. A toxic anemia of severe grade was induced by inoculation of these organisms.

A comparison of the results of chemical analyses of the blood of these experimental animals with similar results on control normal animals, and especially with analogous results obtained in clinical diseases of man, is our purpose in the present communication. The difficulty of applying conceptions derived from animal experimentation at once in clinical medicine is keenly appreciated. Nevertheless, living things have much in common, and the results of animal experimentation have already proved of value in the study of anemia.

In the present study, attention has been devoted especially to that group of experimental animals in which the most striking changes were observed in the blood, namely, the animals inoculated with toxic strains of *C. welchii*. Quantitative chemical analyses of the blood were made in conjunction with other observations on these same animals, recorded in the previous paper. By reference to the protocols there presented, the chemical observations can be fitted into the more complete experimental record.

TECHNIC

Adult male rabbits were used exclusively, and only toxic strains of *C. welchii* were employed. Some of the animals were injected intramuscularly with eighteen hour cultures in anaerobic dextrose broth, in doses of from 0.5 to 1 cc. A severe grade of anemia was induced in these animals in five days. Toxic bacteria-free filtrates made by the method of Bull and Pritchett² and

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1 Patterson, Marjorie B., and Kast, Ludwig. Toxic Anemia Produced by *Clostridium Welchii*, Arch. Path. **5** (March) 1928.

2 Bull, Carroll G., and Pritchett, Ida W. J. Exper. Med. **26** 867, 1917.

employing the broth formula of Kahn and Torrey³ were injected intravenously into rabbits of a second group in initial doses of from 1 to 3 cc., followed in some instances by a second dose on the third or fourth day if further effect was desired

In order to induce more chronic toxemia, rabbits were given repeated intramuscular injections of small quantities of whole culture or intravenous injections of toxic bacteria-free filtrates, the initial dose varying from 0.1 to 0.5 cc. Chemical analyses of the blood of these animals were made from time to time over a period of from one to two months. In conjunction with these observations, blood counts and estimation of hemoglobin by the Dare hemoglobinometer were carried out, usually just before obtaining the blood sample for chemical analyses. Data of these related examinations have been presented in the preceding paper.

In the chemical analyses of the blood, Newcomer's⁴ method for hemoglobin as described by Myers⁵ and Wong's procedure have been utilized, methods which have been found to be the most dependable by Lindsay, Rhee and Selinger.⁶ Figures for hemoglobin thus obtained are presented in the present communication. The Folin-Wu⁷ method was employed for the blood sugar. For cholesterol, the procedure of Myers and Wardell with the modifications suggested by Baumann and Holly⁸ was followed. Trichloroacetic acid was used as the protein precipitant in estimations of the nonprotein nitrogen. The technique outlined by Bernheim⁹ was adopted for the icterus index of the blood serum. With the exception of the icterus index, all analyses were made on oxalated whole blood drawn after an eighteen hour fast.

ANALYTIC RESULTS

The results of blood analyses on control normal rabbits are presented in table 1, together with the maximum, minimum and average values of the series. From sixteen to thirty control animals were examined to establish the average figure, except in the case of the icterus index, for which only six control determinations were made.

It is evident from the table that the control animals showed marked variations in concentration of the blood constituents studied. Nuzum, Osborne and Sansum¹⁰ have shown that the character of the diet influences the level of nonprotein nitrogen and of urea nitrogen in the blood of rabbits. In monthly specimens from control rabbits over a period of

3 Kahn, M. C., and Torrey, J. C. *Proc. Soc. Exper. Biol. & Med.* **22**, 8, 1925.

4 Newcomer, H. S. *J. Biol. Chem.* **37**, 465, 1919.

5 Myers, Victor C. *Practical Chemical Analysis of Blood*, St. Louis, C. V. Mosby Company, 1924.

6 Lindsay, J. W., Rhee, C. E., and Selinger, M. A. *J. Lab. & Clin. Med.* **11**, 737, 1926.

7 Folin, O., and Wu, H. *J. Biol. Chem.* **41**, 367, 1920.

8 Baumann, E. J., and Holly, O. M. *J. Biol. Chem.* **55**, 457, 1923.

9 Bernheim, A. R. *Icterus Index (A Quantitative Estimation of Bilirubinemia)*, *J. A. M. A.* **82**, 291 (Jan. 26), 1924.

10 Nuzum, F. R., Osborne, M., and Sansum, W. D. *Experimental Production of Hypertension*, *Arch. Int. Med.* **35**, 492 (April), 1925.

a year these authors observed variations in urea nitrogen of the blood from 14 to 23 mg and in nonprotein nitrogen from 32 to 38 mg per hundred cubic centimeters. In experimental animals fed on a high protein diet for twelve months they observed an increase in both nonprotein and urea nitrogen of more than 100 per cent above the level of the controls, and in these animals there were evident renal lesions. Horvath¹¹ has reported figures for urea nitrogen of the blood of rabbits on a diet of millet and cabbage, varying from 13 to 25 mg per hundred cubic centimeters. In general, our rabbits received a diet of cabbage

TABLE 1—*Analyses of Control Specimens of Rabbit Blood*

| Rabbit | Hemo- globin, Gm per 100 Cc | Red Cells, Millions per C mm | Color Index | Non protein Nitrogen, Mg per 100 Cc | Urea Nitro- gen, Mg per 100 Cc | Urea N N P N Ratio | Amino Acid Nitrogen, Mg per 100 Cc | Sugar, Mg per 100 Cc | Choles- terol Mg per 100 Cc |
|---------|---|--|----------------|---|--|--------------------------|--|-------------------------------|---|
| 3 | 12.7 | 6.28 | 0.62 | 44.2 | 13.5 | 0.30 | 9.1 | 205 | 79 |
| 4 | 13.4 | 4.74 | 0.87 | 39.1 | 16.4 | 0.42 | 8.7 | 136 | 70 |
| 5 | 11.8 | 6.22 | 0.53 | 36.7 | | | | | 62 |
| 6 | 12.5 | 7.02 | 0.55 | 41.3 | | | | 106 | 67 |
| 7 | 10.8 | 6.76 | 0.66 | 46.4 | | | | 172 | 38 |
| 8 | 9.2 | 5.20 | 0.53 | 37.0 | 14.0 | 0.37 | 8.5 | 150 | 68 |
| 9 | 13.4 | 7.38 | 0.56 | 36.2 | 10.7 | 0.29 | 10.3 | 135 | 91 |
| 33 | 7.6 | 7.44 | 0.31 | 37.5 | 15.8 | 0.42 | 6.5 | | 69 |
| 58 | 11.2 | 5.84 | 0.58 | 40.8 | 12.3 | 0.30 | | 115 | 68 |
| 59 | 11.8 | 5.84 | 0.62 | 42.3 | 20.2 | 0.47 | | 103 | 72 |
| 60 | 10.9 | 5.84 | 0.56 | 43.3 | 16.9 | 0.39 | | 130 | 87 |
| 61 | 11.3 | 4.50 | 0.67 | 45.4 | 15.9 | 0.35 | | 109 | 86 |
| 62 | 12.7 | 6.62 | 0.59 | 42.3 | 10.4 | 0.24 | | 109 | 66 |
| 63 | 12.8 | 6.62 | 0.59 | 39.4 | 20.2 | 0.51 | | 120 | 57 |
| 64A | 11.7 | 7.28 | 0.49 | 46.0 | 18.7 | 0.40 | 6.8 | 119 | 59 |
| 65 | 10.6 | 7.20 | 0.44 | 42.6 | 20.2 | 0.47 | | 107 | 92 |
| 66 | 10.7 | 6.90 | 0.47 | 52.1 | 26.7 | 0.51 | | 123 | 74 |
| 67 | 11.0 | 5.12 | 0.65 | 49.9 | 24.2 | 0.44 | | 107 | 87 |
| 68 | 12.1 | 7.26 | 0.51 | 38.6 | 14.2 | 0.27 | 6.5 | 118 | 108 |
| 69 | 11.2 | 7.20 | 0.47 | 40.3 | 10.8 | 0.26 | 8.2 | 144 | 65 |
| 70 | 10.9 | 7.40 | 0.44 | 34.5 | 11.7 | 0.33 | 6.6 | 140 | 64 |
| 71 | 11.8 | 6.60 | 0.54 | 40.0 | 14.0 | 0.35 | 7.4 | 187 | 94 |
| 72 | 14.8 | 6.20 | 0.72 | 43.0 | 10.0 | 0.23 | 8.7 | 194 | 75 |
| 73 | 11.1 | 6.54 | 0.52 | 37.5 | 9.6 | 0.25 | 8.4 | 111 | 81 |
| 74 | 8.9 | 6.64 | 0.40 | 38.8 | 14.1 | 0.36 | 9.9 | 150 | 87 |
| 75 | 10.0 | 5.86 | 0.52 | 30.2 | 8.2 | 0.27 | 9.7 | 111 | 96 |
| 76 | 10.2 | 5.97 | 0.52 | 34.6 | 12.8 | 0.37 | 10.9 | 125 | 59 |
| 79 | 12.1 | 5.78 | 0.64 | 49.1 | 18.4 | 0.37 | 8.2 | 125 | 75 |
| 90 | | 5.24 | | | | | | 99 | 61 |
| 91 | | 5.08 | | | | | | 79 | 68 |
| Maximum | 14.8 | 7.44 | 0.87 | 52.1 | 26.7 | 0.47 | 10.9 | 205 | 105 |
| Minimum | 7.6 | 4.50 | 0.31 | 39.2 | 8.2 | 0.23 | 6.5 | 79 | 37 |
| Average | 11.4 | 6.37 | 0.55 | 41.3 | 15.1 | 0.35 | 8.3 | 152 | 73 |

supplemented occasionally with carrots, oats and hay. Animals subjected to acute intoxication experiments received cabbage exclusively, beginning two days before the first inoculation. In the twenty-five control observations on urea nitrogen shown in table 1, the value ranges from 8.2 to 26.7 with an average of 15.1 mg per hundred cubic centimeters of blood. For normal human blood Myers¹² gives from 10 to 15 mg of urea nitrogen per hundred cubic centimeters, and Kast and Wardell¹³ have

11 Horvath, A. A. J. Biol. Chem. 68:343, 1926.

12 Myers, V. C. Physiol. Rev. 4:274, 1924.

13 Kast, L., and Wardell, E. L. Urea in Human Blood, Arch. Int. Med. 22:581 (Nov.) 1918.

recognized 20 mg per hundred cubic centimeters as the upper normal limit for hospital patients. In respect to nonprotein nitrogen, the maximum variation in table 1 is from 30.2 to 52.1 mg per hundred cubic centimeters. Only six rabbits gave figures above 45 mg. The hemoglobin content of the blood of these control rabbits varied from 7.6 to 14.8 Gm with an average of 11.04 Gm per hundred cubic centimeters.

The results of chemical analyses of the blood of rabbits recently infected by injection of whole broth cultures of *C. welchii* are set forth in table 2. Most striking is the decrease in the hemoglobin accompanied by a

TABLE 2—*Biochemical Determinations Made on the Blood of Rabbits in Which an Acute Infection Was Produced with Whole Broth Cultures of (Groups 1 and 2) Strains of C. welchii*

| Rabbit | Day of Treatment | Dose, Cc | Hemoglobin, Gm per 100 Cc | Red Cells, Millions per Cmm | Color Index | Nonprotein Nitrogen, Mg per 100 Cc | Urea Nitrogen, Mg per 100 Cc | Sugar, Mg per 100 Cc | Cholesterol, Mg per 100 Cc |
|--------|------------------|----------|---------------------------|-----------------------------|-------------|------------------------------------|------------------------------|----------------------|----------------------------|
| 64A | Normal | | 11.7 | 7.28 | 0.49 | 46.0 | 18.7 | 119 | 59 |
| | 1 | 0.5 | | | | | | | |
| | 3 | None | 8.9 | 3.78 | 0.72 | 42.8 | 14.7 | 147 | 44 |
| | 4 | 0.3 | | | | | | | |
| | 6 | None | 4.2 | 1.08 | 1.25 | 38.7 | 14.9 | 147 | 51 |
| 66 | Normal | | 10.7 | 6.90 | 0.47 | 52.1 | 26.7 | 123 | 74 |
| | 1 | 0.5 | | | | | | | |
| | 3 | None | 8.4 | 3.80 | 0.67 | 45.8 | | 158 | 60 |
| | 5 | None | 3.3 | 1.58 | 0.66 | 62.5 | 29.5 | 146 | 91 |
| 65 | Normal | | 10.6 | 7.20 | 0.44 | 42.6 | 20.2 | 107 | 92 |
| | 1 | 0.5 | | | | | | | |
| | 3 | None | 7.9 | 3.76 | 0.64 | 39.7 | | 125 | 62 |
| | 4 | 0.3 | | | | | | | |
| | 6 | None | 5.1 | 3.60 | 0.43 | 39.1 | 25.6 | 76 | 87 |
| | 8 | None | 4.9 | 3.74 | 0.40 | 54.0 | 30.6 | 125 | 97 |
| 63 | Normal | | 12.8 | 6.62 | 0.59 | 39.4 | 20.2 | 120 | 57 |
| | 1 | 0.5 | | | | | | | |
| | 3 | None | 7.7 | 5.06 | 0.47 | 35.2 | | 150 | 54 |
| | 4 | 0.3 | | | | | | | |
| | 6 | None | 6.5 | 4.40 | 0.44 | 45.1 | 19.0 | 136 | 82 |
| | 8 | None | 6.2 | 4.40 | 0.43 | 48.7 | 19.9 | 115 | 77 |
| 68 | Normal | | 12.1 | 7.26 | 0.51 | 35.6 | 14.2 | 118 | 108 |
| | 1 | 0.5 | | | | | | | |
| | 3 | None | 8.7 | 5.40 | 0.49 | 43.3 | 15.5 | 161 | 75 |

somewhat more marked diminution in the number of circulating erythrocytes. In specimens of blood obtained by puncture of the ear vein of rabbits, Bushnell and Bangs¹⁴ found an average normal erythrocyte count of 5,988,500 per cubic millimeter. Extreme variations from 4,322,000 to 6,976,000 were observed in a series of hourly observations on one normal rabbit. A red cell count below 4,307,000 per cubic millimeter in rabbits is considered pathologic by these authors. Control counts made by a similar procedure on rabbits used in the present investigation gave an average figure of 6,250,000 with extremes of 9,020,000 and 4,500,000 per cubic millimeter in sixty-eight observations. The figure for the rabbit is higher than the erythrocyte count in human

blood The hemoglobin content, however, is in general lower in rabbits than in man, so that the color index calculated on the same basis as in human blood is normally less than unity in these animals, varying from 0.31 to 0.87, with an average of 0.55 in the control observations In the experimental animals, erythrocyte counts as low as 1,080,000 and 1,580,000 were observed, with a reduction of the hemoglobin to 4.2 and 3.3 Gm per hundred cubic centimeters, respectively, and a rise in the color index as high as 1.25 in the first instance (rabbit 64 A) These striking effects on the erythrocytes have been set forth in the preceding paper¹ It is, however, necessary to recall them here, because of the relation of changed cell concentration to the concentration of other constituents of the blood resulting from uneven distribution of these constituents in the cells and the plasma The other analytic results are less striking on first inspection The nonprotein nitrogen tended to diminish in the first few days, in all except rabbit 68 This change would appear to depend on the reduction in the number of erythrocytes, for Folin and Berglund¹⁵ have demonstrated a greater concentration of nonprotein nitrogen in the corpuscles as compared with the plasma of blood, the difference being due to an excess of rest nitrogen in the cells On the other hand, urea nitrogen is almost evenly distributed in the substance of corpuscles and plasma, and its concentration in whole blood is influenced little by changes in the number or volume of the cells Folin,¹⁶ discussing nonprotein nitrogen of human blood, states that, under normal conditions, the urea nitrogen forms from 35 to 55 per cent of the nonprotein nitrogen, most frequently from 40 to 50 per cent

If one assumes, therefore, that the blood of rabbit 64 A before inoculation contained equal volumes of plasma and corpuscles and that $\frac{2}{5}$ of the nonprotein nitrogen, or 18 mg, was in the plasma and $\frac{3}{5}$, or 28 mg, in the corpuscles, it would appear that reduction of the corpuscles to 3,780,000 per cubic millimeter caused the plasma to constitute $\frac{3}{4}$ of the blood volume and the corpuscles $\frac{1}{4}$ Of the observed nonprotein nitrogen, namely, 42.8 mg per hundred cubic centimeters, the indicated partition between plasma and cells would be in the ratio of $\frac{2}{5} \times \frac{3}{4}$ $\frac{3}{5} \times \frac{1}{4}$ or $\frac{6}{20}$ $\frac{3}{20}$ or 2:1 Two thirds of the observed 42.8 mg, or 29.5 mg, would therefore represent the nonprotein nitrogen of the plasma at this time a distinct increase over the normal figure of 18 mg before inoculation In the same way, the observation on the sixth day in rabbit 64 A, namely 33.7 mg nonprotein nitrogen per hundred cubic centimeters of blood, requires elucidation At this time, the corpuscles numbered 1,080,000 per cubic millimeter, or approximately $\frac{10}{67}$ of their number before inoculation, so that they now made up about $\frac{1}{13}$ of

15 Folin, O., and Berglund, H. *J Biol Chem* **51** 418, 1922

16 Folin, O. *Physiol Rev* **2** 460, 1922

the volume of the blood. The observed nonprotein nitrogen, on this assumption, would be partitioned between plasma and corpuscles in the ratio of $\frac{12}{13} \times \frac{2}{5} \times \frac{1}{13} \times \frac{3}{5}$ or $\frac{24}{65}$ or 8:1. Eight ninths of the observed nonprotein nitrogen (33.7), or 30 mg, would represent the nonprotein nitrogen of the plasma at this time. While these calculations are not considered precisely accurate as representing actual conditions in the blood of this experimental animal, they, nevertheless, indicate definitely that the nonprotein nitrogen of the plasma has been increased during the course of the experimental disease. In some instances, as in rabbits 66, 65, 63 and 68, the nonprotein nitrogen of even the whole blood rose above the level observed before inoculation. It would, therefore, appear that the acute infection with *C. welchii* has caused an increased accumulation of intermediate nitrogenous catabolic substances in the blood, not yet transformed into the more normal excretory products such as urea.

The figures for urea nitrogen in this group of rabbits with acute infection are extremely variable. Without data concerning the urinary urea, one hesitates to interpret the figures for blood urea. However, it would appear that injury to the kidney may have been responsible for a moderate retention of urea in some of these animals, as for example in rabbit 65.

Bacteria-free toxic filtrates of cultures of *C. welchii* were injected into six rabbits so as to cause severe acute disturbances. The results of chemical analyses of the blood of these animals are shown in table 3. Here also the most striking feature is the marked diminution in the number of circulating erythrocytes and the corresponding but in general somewhat less marked reduction of hemoglobin in the blood. The consequent rise in the color index would appear to be a fairly characteristic feature of this toxic anemia. In these six animals, the nonprotein nitrogen acted much as in the preceding group, illustrated in table 2, again indicating an accumulation in the blood of intermediate nonprotein products of nitrogen catabolism. Rabbit 75 behaved in an exceptional manner, the marked retention of nonprotein nitrogen, of urea, of sugar and of cholesterol indicating severe impairment of renal function. This animal was killed on the fifth day, and histologic examination of the kidneys revealed an acute hemorrhagic and hemoglobinuric nephritis, distinctly more severe than the morphologic changes in the other animals of this group studied in the same way.

Milder, chronic infections with *C. welchii* were induced in six rabbits by the repeated injection of small doses of whole broth cultures of *C. welchii* over a period of from twenty-nine to fifty days. The results of blood analyses on these animals are shown in table 4. The reduction in erythrocytes and in hemoglobin was less in these animals, and after three

or four weeks, in spite of continued inoculations there was a tendency toward restoration to normal. The chemical analyses were begun early in the third week of the treatment. Except for hemoglobin and red blood cells the figures remain within the limits of observations on normal control animals. These observations are in accord with other evidence of an acquired immunity in these animals.

Toxic, bacteria-free filtrates of cultures of *C. welchii* were injected in divided doses into six rabbits over periods of from forty-eight to

TABLE 3—*Biochemical Determinations Made on the Blood of Rabbits in Which an Acute Severe Toxemia Was Induced with Toxic Filtrates of (Groups 1 and 2) Strains of C. welchii*

| Rabbit | Day of Treatment | Dose, Cc | Hemoglobin, Gm per 100 Cc | Red Cells, Millions per Cmm | Color Index | Nonprotein Nitrogen, Mg per 100 Cc | Urea Nitrogen, Mg per 100 Cc | Sugar, Mg per 100 Cc | Cholesterol, Mg per 100 Cc |
|--------|------------------|----------|---------------------------|-----------------------------|-------------|------------------------------------|------------------------------|----------------------|----------------------------|
| 71 | Normal | | 11.8 | 6.60 | 0.54 | 40.0 | 14.0 | 187 | 94 |
| | 1 | 1.0 | | | | | | | |
| | 3 | 1.5 | 7.3 | 3.82 | 0.57 | 50.0 | 13.0 | 142 | 76 |
| | 4 | 2.0 | | | | | | | |
| | 6 | None | 5.2 | 2.44 | 0.64 | 43.5 | 10.5 | 162 | 53 |
| 74 | Normal | | 8.9 | 6.64 | 0.40 | 38.8 | 14.1 | 150 | 57 |
| | 1 | 2.5 | | | | | | | |
| | 3 | 2.5 | 3.0 | 2.14 | 0.42 | 31.4 | 13.2 | 174 | 63 |
| | 4 | 3.0 | | | | | | | |
| | 5 | None | 4.1 | 1.60 | 0.78 | 53.6 | 14.5 | 159 | 128 |
| 75 | Normal | | 10.0 | 5.86 | 0.52 | 30.2 | 8.2 | 111 | 96 |
| | 1 | 2.0 | | | | | | | |
| | 3 | None | 5.4 | 2.80 | 0.39 | 103.4 | 71.3 | 157 | 93 |
| | 4 | 2.0 | | | | | | | |
| | 5 | None | 4.4 | 1.80 | 0.72 | 156.2 | 106.0 | 170 | 153 |
| 76 | Normal | | 10.2 | 5.90 | 0.32 | 34.6 | 12.8 | 125 | 59 |
| | 1 | 2.5 | | | | | | | |
| | 3 | 3.0 | 6.2 | 2.88 | 0.67 | 42.0 | 14.7 | 133 | 123 |
| | 4 | 3.0 | | | | | | | |
| | 5 | None | 5.3 | 2.00 | 0.80 | 37.0 | 14.8 | 170 | 107 |
| 28 | Normal | | | 5.02 | | | | | |
| | 1 | 2.0 | | | | | | | |
| | 2 | 2.0 | | | | | | | |
| | 3 | 3.0 | | | | | | | |
| | 5 | None | 4.7 | 2.58 | 0.56 | 52.3 | 19.1 | | 107 |
| 29 | Normal | | | 6.00 | | | | | |
| | 1 | 3.0 | | | | | | | |
| | 2 | 3.0 | | | | | | | |
| | 3 | 5.0 | | | | | | | |
| | 5 | 5.0 | | | | | | | |
| | 6 | None | 5.8 | 3.22 | 0.54 | 58.5 | 19.3 | | 86 |

seventy-eight days in the attempt to induce a chronic toxic anemia. Chemical analyses of the blood were undertaken only at the end of each experiment on killing the animal, at a time when the earlier reduction of hemoglobin and of red blood cells had been partly restored toward normal. The results are shown in table 5. The figure for urea nitrogen remained below 20 mg. in all except rabbit 17, whereas the amount of nonprotein nitrogen tended to be high in all except rabbit 15. In the average figures for all six animals the urea nitrogen constituted 31.8 per cent of the nonprotein nitrogen. Here again there is an indication

TABLE 4—*Biochemical Determinations Made on the Blood of Rabbits in Which a Chronic Infection Was Produced with Whole Broth Cultures of (Groups 1 and 2) Strains of C welchii*

| Rabbit | Day of Treatment | Dose, Cc | Hemoglobin, Gm per 100 Cc | Red Cells, Millions per C mm | Color Index | Nonprotein Nitrogen, Mg per 100 Cc | Urea Nitrogen, Mg per 100 Cc | Sugar, Mg per 100 Cc | Cholesterol, Mg per 100 Cc |
|--------|------------------|----------|---------------------------|------------------------------|-------------|------------------------------------|------------------------------|----------------------|----------------------------|
| 58 | Normal | | 11.2 | 5.81 | 0.58 | 10.8 | 12.3 | 115 | 68 |
| | 1 | 0.3 | | | | | | | |
| | 3 | 0.3 | | | | | | | |
| | 7 | 0.3 | | | | | | | |
| | 9 | 0.2 | | | | | | | |
| | 13 | 0.2 | | | | | | | |
| | 15 | None | 10.2 | 4.04 | 0.77 | 37.7 | 8.8 | 141 | 65 |
| | 20 | 0.2 | | | | | | | |
| | 22 | None | 9.4 | 4.73 | 0.60 | 27.5 | 10.6 | 122 | 78 |
| | 28 | 0.5 | | | | | | | |
| | 30 | None | 8.2 | 4.78 | 0.53 | 35.2 | | 96 | 72 |
| | 31 | 0.5 | | | | | | | |
| | 36 | 0.5 | 7.4 | 3.76 | 0.60 | 31.6 | 8.3 | 122 | 78 |
| | 43 | 1.0 | 9.6 | 5.48 | 0.48 | 46.8 | 17.8 | 103 | 61 |
| | 50 | None | 9.0 | 5.30 | 0.51 | 34.5 | 8.9 | 161 | 66 |
| 69 | Normal | | 11.2 | 7.20 | 0.47 | 10.3 | 10.8 | 144 | 65 |
| | 1 | 0.5 | | | | | | | |
| | 9 | 0.3 | | | | | | | |
| | 12 | 0.3 | | | | | | | |
| | 15 | None | 11.1 | 4.62 | 0.78 | 31.4 | 9.1 | 111 | 86 |
| | 22 | 0.5 | 9.3 | 5.08 | 0.57 | 51.7 | 10.7 | 166 | 65 |
| | 24 | 0.5 | | | | | | | |
| | 29 | None | 9.7 | 5.26 | 0.56 | 32.0 | 8.3 | 147 | 80 |
| 25 | Normal | | | 5.96 | | | | | |
| | 37 | 4.0 | 9.8 | 5.26 | 0.57 | 25.2 | 16.0 | | 73 |
| 60 | Normal | | 10.9 | 5.81 | 0.76 | 43.3 | 16.9 | 130 | 87 |
| | 1 | 0.1 | | | | | | | |
| | 3 | 0.1 | | | | | | | |
| | 6 | 0.1 | | | | | | | |
| | 15 | None | 6.1 | 3.20 | 0.60 | 42.8 | 14.8 | 86 | 59 |
| | 20 | 0.1 | | | | | | | |
| | 22 | None | 6.7 | 4.18 | 0.50 | 27.9 | 10.4 | 132 | 67 |
| | 28 | 0.2 | | | | | | | |
| | 30 | None | 7.0 | 4.58 | 0.46 | 42.6 | | 56 | 82 |
| | 31 | 0.2 | | | | | | | |
| | 36 | None | 11.1 | 4.02 | 0.85 | 37.2 | 7.8 | 115 | 102 |
| 61 | Normal | | 11.3 | 4.50 | 0.76 | 45.4 | 15.9 | 109 | 86 |
| | 1 | 0.1 | | | | | | | |
| | 3 | 0.1 | | | | | | | |
| | 6 | 0.1 | | | | | | | |
| | 13 | 0.1 | | | | | | | |
| | 16 | None | 7.2 | 3.06 | 0.73 | 33.8 | 10.2 | 144 | 86 |
| | 20 | 0.1 | | | | | | | |
| | 22 | None | 6.8 | 4.13 | 0.50 | 32.9 | 10.1 | 167 | 82 |
| | 28 | 0.2 | | | | | | | |
| | 30 | None | 8.3 | 5.64 | 0.41 | 33.8 | | 106 | 114 |
| | 31 | 0.3 | | | | | | | |
| | 36 | 0.5 | 7.8 | 5.34 | 0.44 | 27.6 | 8.2 | 120 | 95 |
| | 43 | 1.0 | 8.5 | 4.46 | 0.59 | 45.1 | 15.7 | 107 | 92 |
| | 50 | None | 8.2 | 4.76 | 0.53 | 31.7 | 9.5 | 220 | 68 |
| 70 | Normal | | 10.9 | 7.40 | 0.44 | 34.5 | 11.7 | 140 | 61 |
| | 1 | 0.1 | | | | | | | |
| | 9 | 0.1 | | | | | | | |
| | 12 | 0.1 | | | | | | | |
| | 15 | None | 8.3 | 3.40 | 0.73 | 31.8 | 10.0 | 99 | 117 |
| | 22 | 0.3 | 8.6 | 3.92 | 0.66 | 43.7 | 8.7 | 122 | 61 |
| | 29 | None | 10.2 | 5.04 | 0.62 | 65.8 | 33.1 | 109 | 90 |

of relative increase in nonprotein nitrogen other than urea, which is in accord with the observations on the more severe acute intoxications in rabbits

Kahn and Barsky¹⁷ have recorded figures for some of the blood constituents in three cases of pernicious anemia. The figures for nonprotein nitrogen ranged from 29.3 to 38.5 mg per hundred cubic centimeters, for urea nitrogen from 18.4 to 20.1 mg. In all three cases, the urea nitrogen formed more than one half of the nonprotein nitrogen, which might be expected in conditions in which the blood cells are diminished. Gettler and Lindeman¹⁸ have presented data on chemical analyses of blood in thirty-two cases of pernicious anemia, including eighty-seven complete blood analyses. They found the nonprotein nitrogen of the blood increased above the normal limits (25 to 40 mg) in 48 per cent of their cases, an amount too large to be accidental. Urea

TABLE 5—*Biochemical Determinations Made on the Blood of Rabbits After Chronic Intoxications Had Been Produced with Toxic Filtrates of (Groups 1 and 2) Strains of C. welchii*

| Rabbit | Day of Treatment | Total Toxin Given Cc | Hemoglobin, Gm per 100 Cc | Red Cells, Millions per C.mm | Color Index | Nonprotein Nitrogen, Mg per 100 Cc | Urea Nitrogen, Mg per 100 Cc. | Sugar, Mg per 100 Cc | Cholesterol, Mg per 100 Cc |
|--------|------------------|----------------------|---------------------------|------------------------------|-------------|------------------------------------|-------------------------------|----------------------|----------------------------|
| 12 | 73 | 37.5 | 8.6 | 4.62 | 0.56 | 49.5 | 19.0 | | 95 |
| 22 | 47 | 27.25 | 6.0 | 5.44 | 0.33 | 59.0 | 16.4 | | 73 |
| 15 | 50 | 33.4 | 8.9 | 4.98 | 0.55 | 34.6 | 19.2 | 176 | 61 |
| 21 | 49 | 46.5 | 11.0 | 4.98 | 0.68 | 97.4 | 11.7 | | 92 |
| 17 | 78 | 32.4 | 11.6 | 5.40 | 0.65 | 72.1 | 28.1 | | 81 |
| 20 | 28 | 34.5 | 9.1 | 5.32 | 0.51 | 73.4 | 18.8 | | 83 |

nitrogen also tended to be high, but in only 18 per cent of the cases was it above the normal limit of 20 mg. They were inclined to ascribe these relations to the decreased amount of circulating blood and diminished power of oxidation within the cells. The observation of analogous changes in the blood of our rabbits after intoxication with products of *C. welchii* suggests that the increase of nonprotein nitrogen in patients with pernicious anemia as well as in these experimental animals may be due to exaggerated protein catabolism associated with a toxemia, however they are not necessarily of the same causation.

Table 6 presents the results of analyses for amino-nitrogen as determined by Folin's¹⁹ colorimetric method, these were, on the average, slightly higher (0.5 mg) than those obtained by the gasometric pro-

17 Kahn, M., and Barsky, J. Chemistry of Pernicious Anemia, Arch Int Med 23 334 (March) 1919

18 Gettler, A. O., and Lindeman, E. Blood Chemistry of Pernicious Anemia Arch Int Med 26 453 (Oct) 1920

19 Folin, O. J Biol Chem 51:374, 1922

cedure of Van Slyke Greene, Sandiford and Ross²⁰ have reported data on the amino-acid nitrogen of human blood in health and in a variety of pathologic conditions In twenty normal specimens, the figures obtained were, maximum 8, minimum 5.1 and average 6.38 mg per hundred cubic centimeters In the blood of twelve young men after fasting one night, Berglund²¹ found an average amino-acid nitrogen of 6.4 mg per hundred cubic centimeters The figures for the blood of control rabbits

TABLE 6—*Amino-Acid Nitrogen of Blood in Acute and Chronic Intoxications*

| Rabbit | Day of Treatment | Inoculum | Amino-Acid Nitrogen, Mg per 100 Cc |
|-----------------------|------------------|---------------------|---------------------------------------|
| Acute Intoxications | | | |
| 64A | Normal | Whole broth culture | 6.8 |
| | 3 | | 7.0 |
| | 6 | | 6.8 |
| 68 | Normal | Whole broth culture | 6.3 |
| | 3 | | 8.3 |
| 71 | Normal | Toxin | 7.4 |
| | 3 | | 9.0 |
| | 6 | | 8.6 |
| 74 | Normal | Toxin | 9.9 |
| | 3 | | 8.8 |
| | 5 | | 9.2 |
| 75 | Normal | Toxin | 9.7 |
| | 3 | | 8.8 |
| | 5 | | 8.0 |
| 76 | Normal | Toxin | 10.9 |
| | 3 | | 8.0 |
| | 5 | | 8.4 |
| Chronic Intoxications | | | |
| 69 | Normal | Whole broth culture | 8.2 |
| | 15 | | 7.9 |
| | 22 | | 7.8 |
| | 29 | | 7.8 |
| 70 | Normal | Whole broth culture | 6.6 |
| | 15 | | 6.8 |
| | 22 | | 8.2 |
| | 29 | | 8.7 |
| 12 | 73* | Toxin | 8.0 |
| 22 | 47* | Toxin | 9.2 |
| 15 | 50* | Toxin | 7.0 |
| 21 | 49* | Toxin | 8.2 |
| 17 | 78* | Toxin | 9.6 |
| 20 | 48* | Toxin | 10.1 |

* Termination of treatment

in our table 1 are somewhat higher, namely maximum, 10.9, minimum, 6.3, average, 8.3 mg per hundred cubic centimeters Greene, Sandiford and Ross,²⁰ in their exhaustive study of amino-nitrogen of the blood in disease, present figures for six cases of anemia (the type of anemia not stated) ranging from 5.1 to 8, with an average of 6.38 mg per hundred cubic centimeters, identical with their average figure for twenty

20 Greene, C. H., Sandiford, K., and Ross, H. J. Biol. Chem. **58** 845, 1923-1924

21 Berglund, H. Nitrogen Retention in Chronic Interstitial Nephritis, J. A. M. A. **79** 1375 (Oct. 21) 1922

normal specimens of blood. Gettler and Lindeman found abnormally high figures for amino-nitrogen in pernicious anemia, from 9 to 40 mg per hundred cubic centimeters, as determined by Van Slyke's method, at least four times the normal in some cases. In table 6 are presented figures of the amino-nitrogen in the blood of rabbits with experimental anemia induced by injection of cultures or products of *C welchii*. The variations are all within the normal limits for rabbits, as indicated in table 1. In this respect, these rabbits appear to be distinctly different from the patients with pernicious anemia studied by Gettler and Lindeman.

The control specimens of blood showed the greatest variations in the sugar content. These specimens were obtained about eighteen hours after feeding, but, even so, the animals cannot be regarded as in a postabsorptive state. For this purpose, Baumann and Holly⁸ found it necessary to allow a fast of forty-eight hours in rabbits. The figures recorded in tables 2 and 3 show a moderate increase in blood sugar in most of the rabbits after the first injection, with a tendency to decrease subsequently in spite of further inoculations. These changes resemble the alterations in blood sugar observed in acute infections in man. They are not in the same category as the observations of Zeckwer and Goodell,²² who observed rapidly developing hyperglycemia in rabbits after intravenous injection of killed bacteria, with return to normal in a few hours. Such rapid fluctuations in our animals would have escaped detection.

The blood cholesterol of thirty control rabbits shown in table 1 averaged 73 mg per hundred cubic centimeters, near the figure (67 mg) reported by Baumann and Holly⁸ as the average of their observations in seventeen control rabbits. In our series, four rabbits had more than 90 mg of cholesterol per hundred cubic centimeters of blood, and one animal had 108 mg. These specimens were obtained by heart puncture during brief ether anesthesia, and it is believed that the anesthesia could not have influenced the cholesterol observations, as Mahler²³ found the blood cholesterol to be significantly altered only after from fifteen to twenty minutes of deep anesthesia.

The cholesterol of human blood is much reduced during acute bacterial infections. Chauffard²⁴ has observed reduction of the cholesterol content of the suprarenals in pulmonary tuberculosis, tuberculous meningitis, pneumonia, typhoid fever and septicemia. In all types of anemia in man, the blood cholesterol is diminished. As the patient

22 Zeckwer, I. T., and Goodell, H. J. *Exper. Med.* **42**: 43, 1925.

23 Mahler, A. *J. Biol. Chem.* **69**: 653, 1926.

24 Chauffard, quoted by Campbell, J. M. H. *Quart. J. Med.* **18**: 393, 1924-1925.

recovers from the anemia or from the infection, the cholesterol increases. Horiuchi²⁵ produced experimental anemia in rabbits on a fat-free diet by repeated withdrawal of from 10 to 15 cc of blood over a period of from five to seventeen days. In these animals, he observed an initial slight decrease of blood cholesterol followed by an increase to two or three times the normal control. Of our nine rabbits recorded in tables 2 and 3, one animal (no. 71) showed a progressive decrease of blood cholesterol, but in the others the initial decrease was followed by a subsequent increase. The decrease here was greater than that observed by Horiuchi, possibly because a more severe anemia was produced. The subsequent increase was, however, less than that described by him, and in no instance did the blood show evidence of a gross lipemia. In the rabbits subjected to a more prolonged mild intoxication, as recorded in table 4, the decrease in cholesterol also occurred, followed by a more definite indication of the rise in blood cholesterol in the later period of treatment. The evident immunity acquired by rabbits during administration of whole broth cultures or of toxic filtrates of *C. welchii* for a period of twenty-five days or longer, as shown by Patterson and Kast¹ in a previous paper, may be correlated with this rise in the blood cholesterol.

The icterus index of rabbit's blood is much lower than that of human blood, the latter ranging from 4 to 6 by Bernheim's technic. In six control rabbits, the icterus index ranged from 1.5 to 2.2 with an average of 1.95. In the experimental animals, particularly in those subjected to severe acute intoxication, the blood serum was often tinged with hemoglobin because of the violent hemolysis *in vivo*, and an estimation of the icterus index could not be made. The observations made at other times are recorded in table 7. Here it will be seen that the icterus index was found always to be above the upper extreme for the controls except in one observation made on rabbit 10 on the fifty-second experimental day. The highest value was 12.5 in rabbit 84 on the fifth day of treatment. Bernheim⁹ has found that the icterus index varies from 6.5 to 12.5 with an average of 10 in pernicious anemia of man, while in secondary anemia her figures ranged from 2.3 to 3.9 with an average of 3.3. Taking into account the normally lower icterus index of the rabbit, the proportionate increase from 1.5 to 6 times the control figure in these experimental animals would appear to correspond closely with the elevation of the icterus index observed by Bernheim in human pernicious anemia. The phenomenon is not, however, a specific reaction to *C. welchii* in a bacteriologic sense, for a similar, if less marked, rise in the icterus index was observed in rabbits 87 and 71, which were treated with cultures of other intestinal anaerobes.

25 Horiuchi, Y. J. Biol. Chem. **44** 347, 1920.

TABLE 7—*Determination of the Icterus Index in the Blood of Rabbits in Which Acute and Chronic Intoxications Had Been Produced with C welchii*

| Rabbit | Day of Treatment | Inoculum | Icterus Index |
|-----------------------|------------------|------------------------|---------------|
| Acute Intoxications | | | |
| 28 | 5 | Toxin | 3.0 |
| 29 | 6 | Toxin | 3.8 |
| 32 | 5 | Toxin | 8.0 |
| 33 | 5 | Toxin | 2.8 |
| 34 | 5 | Toxin | 12.5 |
| 36 | 6 | Toxin | 4.5 |
| 37 | 6 | Toxin | 6.5 |
| Chronic Intoxications | | | |
| 17 | 46 | Toxin | 2.4 |
| 20 | 46 | Toxin | 2.6 |
| 15 | 49 | Toxin | 3.0 |
| 21 | 49 | Toxin | 3.1 |
| 12 | 42 | Toxin | 4.5 |
| 22 | 48 | Toxin | 2.6 |
| 23 | 23 | Toxin | 5.3 |
| 10 | 52 | Whole broth culture | 1.7 |
| 18 | 33 | Whole broth culture | 3.8 |
| 25 | 33 | Whole broth culture | 4.4 |
| 19 | 73 | Whole broth culture | 3.5 |
| Control Rabbits | | | |
| 13 | 37 | C bifermentans culture | 3.5 |
| 14 | 71 | C sporogenes culture | 2.7 |

TABLE 8—*Urobilin Excretion in Rabbits in Which Acute and Chronic Intoxications Had Been Produced with C welchii*

| Rabbit | Day of Treatment | Inoculum | Urobilin, Mg per 100 Cc |
|-----------------------|------------------|------------------------|-------------------------|
| Acute Intoxications | | | |
| 32 | 7 | Whole broth culture | 94.0 |
| 24 | 5 | Whole broth culture | 153.0 |
| 64A | 5 | Whole broth culture | Trace |
| | 6 | | 183.0 |
| 66 | 5 | Whole broth culture | 188.0 |
| 7 | 6 | Whole broth culture | 189.0 |
| 68 | 3 | Whole broth culture | Trace |
| | 4 | | 23.5 |
| | 5 | | 23.5 |
| | 6 | | 62.6 |
| 28 | 5 | Toxin | Trace |
| 27 | 5 | Toxin | 189.0 |
| 29 | 6 | Toxin | 710.4 |
| 71 | 3 | Toxin | Trace |
| | 6 | | 11.1 |
| 74 | 5 | Toxin | Trace |
| 76 | 3 | Toxin | Trace |
| | 5 | | Trace |
| 82 | 6 | Toxin | 47.0 |
| 86 | 6 | Toxin | Trace |
| 87 | 6 | Toxin | 12.0 |
| Chronic Intoxications | | | |
| 21 | 49 | Toxin | Trace |
| 23 | 31 | Toxin | 11.8 |
| 11 | 63 | Whole broth culture | 47.6 |
| 18 | 33 | Whole broth culture | 94.0 |
| 19 | 4 | Whole broth culture | 83.17 |
| | 6 | | 176.35 |
| | 19 | | 118.1 |
| 61 | 29 | Whole broth culture | Trace |
| 69 | 15 | Whole broth culture | Trace |
| 70 | 29 | Whole broth culture | Trace |
| Control Rabbit | | | |
| 6 | 20 | C bifermentans culture | 47.25 |

An estimate of the rate of destruction of red blood cells can also be obtained from the urobilin output in the urine. This was determined by the method of Elman and McMaster²⁶ at intervals during the experimental treatment, on catheterized specimens of urine obtained from several of the rabbits and on urine removed from the bladder at autopsy on the same animals as well as on a larger number of others. In table 8, in which these values are presented, the latest experimental day on which an analysis is recorded is the day of death of the animal in each instance, and the value recorded for that day was found on analysis of the urine in the bladder at autopsy. Amounts of less than 3 mg of urobilin per hundred cubic centimeters are recorded as "trace." The enormous variations shown in table 8 appear to be definitely correlated with variations in the process of erythrocyte destruction and apparently a more accurate measure of this than is the icterus index. Thus, rabbit 28 had a trace of urobilin in the urine and an icterus index of 3 on the fifth day of treatment, while rabbit 29 had 710 mg of urobilin per hundred cubic centimeters of urine with an icterus index of 38 on the sixth experimental day. Evidently the icterus index is a measure of pigments circulating in the blood, while the urobilin figures represent pigments of hemolytic origin excreted through the bile ducts, transformed in the intestine, resorbed and excreted in the urine. The latter mode of disposition of the pigment products of hemolysis appears to be the chief normal mechanism and to be capable of extremely wide adaptation to the demands made on it by excessive blood destruction. In otherwise normal animals subjected to experimental hemolytic intoxication, the urobilin excretion would appear the better measure of this particular effect.

SUMMARY

1 Acute intoxication of rabbits with the products of *Clostridium welchii* resulted in a marked reduction in hemoglobin and an even greater reduction in the number of erythrocytes of the circulating blood.

2 In most of these animals there was an increase in the nonprotein nitrogen of the blood plasma without a corresponding increase in urea nitrogen, and hence a diminished ratio of the latter to the former. This alteration appears to be a result of abnormal protein catabolism associated with the intoxication.

3 The amino-nitrogen of the blood of the experimental animals, including those with severe acute as well as the more chronic intoxications, did not vary beyond the normal limits observed in control rabbits.

4 The blood sugar rose slightly in the acute intoxications, reaching its maximum about the third day and then subsiding in spite of further inoculations.

26 Elman, R., and McMaster, P. D. J. Exper. Med. **41** 503, 1925.

5 The blood cholesterol tended to diminish in the early stages of the experimental intoxication and to increase subsequently, especially in the animals in which the erythrocytes and hemoglobin tended to return to normal

6 The icterus index of the blood serum in the experimental animals was increased from 1.5 to 6 times the control figures. This change was most evident when rapid destruction of erythrocytes occurred

7 The urobilin output in the urine varied from a trace to 710 mg per hundred cubic centimeters, the large amounts being excreted after active destruction of blood

8 Many of these changes resemble changes observed in anemia in man

THE NONPROTEIN SULPHUR OF THE BLOOD IN CERTAIN PATHOLOGIC CONDITIONS *

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In this paper we have collected the results of a considerable number of observations made on the distribution of the nonprotein sulphur of the blood of normal persons and of persons suffering from various pathologic conditions of the kidneys, heart and liver

Experimental evidence is available which indicates ¹ that nonprotein sulphur exists in blood in the forms of at least three fractions, which appear to possess chemical properties similar to the several classes of sulphur compounds present in urine. Thus, there is present in blood a fraction designated as inorganic sulphate, which is precipitated by the addition of barium chloride to the deproteinized blood filtrate after suitable adjustment of the reaction of the latter. When the deproteinized blood filtrate is heated with acid, an additional precipitation with barium chloride results, and the difference between the value of the total sulphate so obtained and that of the inorganic sulphate is designated as ethereal sulphate. When the deproteinized blood filtrate is treated with a suitable oxidizing agent, certain unoxidized sulphur compounds contained therein are oxidized to sulphate and may be precipitated with barium chloride. The difference between the value for total nonprotein sulphur so obtained and total sulphates is designated as neutral sulphur.

The samples of blood used were obtained from the medical service of the New Orleans Charity Hospital. The analytic methods were those recently described by Denis and Reed ¹. The figures for nonprotein nitrogen were obtained by the method of Folin and Wu ² and those for sodium chloride by the procedure of Whitehorn ³.

The results of the examination of three samples of blood from normal persons (workers in the laboratory) and of thirty-one samples taken from patients in the hospital are given in table 1. In addition to the material contained in this table, we are also in possession of the

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1 Denis, W, and Reed, L. J Biol Chem **71** 191, 1926

2 Folin, V, and Wu, H. J Biol Chem **38** 87, 1919

3 Whitehorn, J. C. J Biol Chem **45** 449, 1920-1921

TABLE 1—*Nonprotein Sulphur in Whole Blood and Plasma*

| Case | men | Mg per 100 Cc. Blood | | Mg per 100 Cc. Blood | | | Mg per 100 Cc. Plasma | | | Diagnosis |
|------|-----|----------------------------------|-------------------------------|---------------------------------|--------------------------------|------------------------------|---------------------------------|--------------------------------|------------------------------|---|
| | | Non- protein Nitro- gen | Sol- dium Chlor- ide | Inor- ganic Sul- phate | Ether- eal Sul- phate | Neu- tral Sul- phur | Inor- ganic Sul- phate | Ether- eal Sul- phate | Neu- tral Sul- phur | |
| 1 | 19 | — | — | 0.28 | 0.34 | 3.73 | 0.51 | 0.95 | 1.27 | Normal |
| 2 | 20 | 34 | — | 0.39 | 0.42 | 3.53 | — | — | 2.14 | Normal |
| 3 | 18 | — | — | 0.45 | 0.15 | 3.24 | 0.85 | 0.91 | 1.72 | Normal |
| 4 | 6 | 41 | 540 | 0.33 | 1.30 | 4.43 | 1.32 | 1.33 | 1.97 | Nephritis, edema Nov 3 1926 |
| | 9 | 39 | 583 | 1.98 | 1.09 | 4.03 | 1.94 | 0.76 | 1.98 | Same patient as above, Jan 28 1927 |
| 5 | 17 | 41 | 506 | 0.34 | 0.96 | 3.49 | 0.65 | 0.66 | 2.57 | Myocardial insufficiency congestive heart failure, April 8 1927 |
| | 14 | 30 | 485 | 0.56 | 0.60 | 3.19 | 1.12 | 0.35 | 2.02 | Same patient as above, March 26, 1927 |
| 6 | 8 | 40 | 502 | 0.45 | 0.84 | 3.01 | 1.48 | 0.24 | 3.18 | Subacute hemorrhagic nephritis |
| 7 | 33 | 35 | 417 | 0.46 | 0.32 | 3.80 | 0.92 | 0.91 | 1.11 | Myocardial insufficiency ascites, congestive heart failure, jaundice |
| 8 | 16 | 67 | 413 | 0.47 | 0.38 | 4.21 | 0.85 | 0.89 | 1.59 | Cardiorenal disease hypertension edema |
| 9 | 13 | 33 | 452 | 0.49 | 0.14 | 3.32 | 0.99 | 0.58 | 1.74 | Asthmatic bronchitis emphysema, chronic nephritis |
| 10 | 23 | 26 | 509 | 0.53 | 0.15 | 4.00 | 1.07 | 0.48 | 1.30 | Eclampsia convulsive |
| 11 | 31 | 32 | 472 | 0.54 | 0.32 | 3.39 | 1.08 | 0.56 | 0.95 | Hyperpiesia, arteriosclerosis, nephritis |
| 12 | 22 | 35 | 484 | 0.55 | 0.54 | 4.59 | 1.03 | 0.31 | 3.29 | Hypertension, arteriosclerosis chronic nephritis |
| 13 | 11 | 50 | 524 | 0.55 | 0.07 | 3.31 | 1.10 | 0.50 | 1.83 | Alcoholic cirrhosis of the liver, jaundice |
| 14 | 24 | 25 | 528 | 0.56 | 0.21 | 2.94 | 1.13 | 1.07 | — | Edema, jaundice |
| 15 | 26 | 37 | 505 | 0.59 | 0.31 | 3.64 | 1.15 | 0.82 | 1.7 | Arteriosclerosis chronic myocarditis, chronic nephritis |
| 16 | 21 | 50 | 484 | 0.60 | 1.33 | 4.95 | 1.17 | 1.39 | 3.21 | Cardiorenal disease hypertension, arteriosclerosis |
| 17 | 29 | 39 | 530 | 0.60 | 0.45 | 3.70 | 1.21 | 0.94 | 1.32 | Hypertension, lesions of the central nervous system due to primary arteriosclerosis |
| 18 | 32 | 41 | 492 | 0.63 | 0.29 | 5.94 | 1.25 | 0.99 | 1.91 | Chronic nephritis hypertension arteriosclerosis |
| 19 | 12 | 74 | 530 | 0.65 | 1.06 | 5.20 | 0.93 | 0.10 | 2.09 | Jaundice, postoperative obstruction |
| 20 | 35 | 52 | 445 | 0.76 | 0.48 | 4.10 | 1.83 | 0.47 | 2.45 | Cardiorenal disease, ascites |
| 21 | 25 | 80 | 403 | 1.09 | 1.15 | 5.01 | 1.61 | 3.31 | 2.24 | Cardiorenal disease hypertension edema and ascites |
| 22 | 27 | 82 | 410 | 1.68 | 0.10 | 4.69 | 3.62 | 0.73 | 0.89 | Nephritis, hypertension, edema, syphilitic aortitis |
| 23 | T | 63 | 644 | 2.55 | 0.58 | 6.23 | 1.56 | 1.45 | 1.27 | Chronic and acute nephritis hypertension and anasarca, July 2, 1926 |
| | 5 | 51 | 789 | 5.32 | 2.54 | 8.99 | 3.69 | 1.62 | 3.27 | Same patient as above July 26, 1926 |
| 24 | 36 | 58 | 494 | 2.88 | 2.04 | 4.17 | 3.00 | 1.72 | 3.83 | Chronic nephritis, hypertension |
| 25 | 2 | 48 | 540 | 3.08 | 1.07 | 2.99 | 2.75 | 1.61 | 1.92 | Cardiorenal disease, hypertension arteriosclerosis |
| 26 | 30 | 60 | 525 | 4.37 | 0.40 | 3.08 | 4.37 | 0.63 | 3.04 | Cardiorenal disease hypertension, arteriosclerosis |
| 27 | 3 | 44 | 491 | 4.72 | 0.93 | 3.51 | 4.53 | 0.63 | 2.27 | Chronic nephritis, hypertension, edema, heart failure |
| 28 | 28 | 91 | 554 | 4.80 | 0.11 | 4.13 | 4.89 | 0.51 | 3.26 | Chronic nephritis hypertension edema |
| 29 | 7 | 175 | 599 | 5.15 | 3.09 | 9.50 | 3.59 | 5.53 | 3.35 | Chronic nephritis uremia |
| 30 | BB | 89 | 466 | 11.0 | 3.35 | 6.07 | 10.95 | — | — | Chronic nephritis congestive heart failure edema |
| 31 | 34 | 188 | 670 | 13.96 | 1.64 | 4.70 | 15.44 | 2.26 | 3.15 | Cardiorenal disease uremia, congestive heart failure |

results obtained with the blood in a series of cases which in number exceeds those presented in the table. As, however, we were unable to obtain in these patients samples of blood of sufficient size for the determination of all of the nonprotein sulphur fractions in both whole blood and plasma, and as the result did not appear to present points of interest not already shown in the tabulated results, we have omitted the presentation of these incomplete analyses.

COMMENT

Within the past five years, several papers have been published on the subject of the concentration of the various nonprotein sulphur fractions of the blood of man. Thus, Meyer-Bisch⁴ determined total (inorganic + ethereal) sulphate in the whole blood of persons suffering from a variety of pathologic conditions. His figures, however, are so much higher than ours that comparison is impossible. Kahn and Postmontier⁵ published an executive series of analyses of the total sulphate and total nonprotein sulphur in normal and pathologic whole

TABLE 2—Results of Determinations of Nonprotein Sulphur Fractions of Normal Persons

| | Whole Blood | Plasma |
|-----------------------------------|-------------|--------|
| Inorganic sulphate, mg per 100 cc | 0.45 | 0.87 |
| Ethereal sulphate, mg per 100 cc | 0.85 | 0.67 |
| Neutral sulphur, mg per 100 cc | 3.80 | 1.95 |

blood, while Loeb and Benedict⁶ made observations on the inorganic sulphate in the serum in a series of cases. In general, the values obtained in the two latter investigations lie within the general range found in our series.

As far as we are aware, analyses other than our own are not available for the nonprotein sulphur of both plasma and whole blood in pathologic conditions.

In a recent paper, two of us⁷ placed on record the results of analyses of nine samples of human blood in which determinations were made of the nonprotein sulphur fractions in whole blood and in plasma of nine normal persons. An average of these results is given in table 2.

While the number of samples from which these average figures were obtained is, of course, too small to give values which might be considered to show the final limits of variation of these fractions under

4 Meyer-Bisch, R. Bio-Chem S **101** 23, 1924.

5 Kahn, G., and Postmontier, R. S. J. Lab & Clin Med **10** 317, 1925.

6 Loeb, R. F., and Benedict, E. M. J. Clin Investigation **4** 33, 1927.

7 Denis, W., and Reed, L. J. Biol Chem **73** 623, 1927.

normal conditions, they serve to indicate the general trend of distribution between plasma and corpuscles. Thus, it will be seen that the inorganic and ethereal sulphate fractions exist in largest amount in the plasma, in fact, if the corpuscles are considered as forming 50 per cent of the value of whole blood it would appear from these figures that the corpuscles may be entirely devoid of inorganic and ethereal sulphate. On the other hand, the neutral sulphur fraction would appear to exist in largest amount, although not exclusively, in the corpuscles.

The results contained in table 1 indicate that there is no relation between the retention of nonprotein nitrogen and of inorganic sulphate, an observation not in accord with those of Loeb and Benedict⁸ or of one of us⁸. Thus, case 30 with a nonprotein nitrogen of 60 mg, shows an inorganic sulphate content of 4.37 mg in the whole blood, whereas case 25, with a nonprotein nitrogen of 80, shows an inorganic sulphur of 1.09. In a series of experiments⁹ on dogs with uraemic nephritis, it was found that the inorganic sulphur fraction of the blood could be strikingly affected by changes in the volume of urine excreted. Thus, in dogs with marked diuresis, the inorganic sulphate of the blood was so reduced that quantitative determination became impossible, whereas with reduction of the output of urine this fraction was much elevated over the normal value.

Most of the patients used in this work had nephritis or cardio-renal disease, and, on looking over the histories, we found that the use of diuretics apparently exerts a profound influence on the level of the inorganic sulphate fraction of blood. Thus, the specimens marked six and nine, respectively, were obtained from the same patient, who had nephritis with generalized edema. Specimen 6 (inorganic sulphate, 0.33 mg, nonprotein nitrogen, 39 mg) was obtained just after treatment with merbaphen, the administration of which had caused marked diuresis, while specimen 9 (inorganic sulphate, 1.98 mg, nonprotein nitrogen, 41 mg) was taken three months later when the patient had again become edematous, with marked reduction in the volume of urine excreted.

Determinations of chloride were made in this series because it seemed possible that fluctuations in the level of inorganic sulphate and of chlorides might run a parallel course. However, this is apparently not the case. As many of these patients had been on salt-free diets for varying lengths of time, it seems possible that different results might be obtained under other dietary conditions.

In normal human blood, the concentration of inorganic sulphate in plasma is usually about double that found in whole blood, as the concentration of this constituent rises, the concentration in the whole blood

8 Denis, W. *J Biol Chem* 49 311, 1921

9 Denis, W., and Reed, L. *J Biol Chem* 73 41, 1927

increases more rapidly than in the plasma, indicating, apparently, the diffusion of sulphate into the normally sulphate-free corpuscles. The result is that in patients showing marked retention the concentration of inorganic sulphate in whole blood and in plasma may be approximately equal. In this connection, it may not be out of place to call attention to the work of DeBoer,¹⁰ who has demonstrated experimentally that at a concentration of carbon dioxide well within physiologic limits the corpuscles of the horse are capable of absorbing sodium sulphate added to blood.

The concentration of ethereal sulphate in normal human blood is, in the majority of specimens examined, considerably greater in plasma than in whole blood, although occasionally the reverse is true. The fluctuations in the figures for this fraction found in the specimen of pathologic blood do not in any way appear to bear a direct relation to the changes observed in the concentration of the inorganic sulphate or of the neutral sulphate fractions. As at present there is no direct evidence to indicate the origin or function of this fraction, speculation on the point would appear fruitless, and we therefore feel justified in merely placing the results on record.

In the normal person, the neutral sulphate fraction appears to be found in greatest concentration in the corpuscles. As shown by the higher values obtained in whole blood as compared to those found in the analysis of plasma, the same general relation appears to hold in the pathologic specimens examined, while with retention of inorganic sulphates concentration of neutral sulphate somewhat above the normal is sometimes found, this is not the rule. In two specimens (numbers 7 and 5), a greatly increased amount of the neutral sulphur fraction was found. Both of these specimens of blood were taken from patients who died a little later, and it is possible that in these cases oxidation within the corpuscles was progressing at a subnormal rate.

CASE HISTORIES IN ABSTRACT

In cases 1, 2 and 3, the subjects were normal young adult males. The histories of the rest of the cases in the order given in table 1 follow.

CASE 4 (laboratory specimens numbers 6 and 9 in table 1)—S. P., a white swamp woodsman, aged 44, came to us with a generalized anasarca, which included puffiness about the eyes. He also complained of frequency of micturition, nocturia, cramps in the legs at night, vertigo, amblyopia, drowsiness and vomiting. The clinical picture suggested a nephritis of the type that causes retention of salt and water. Besides the evidence substantiating the complaints, pallor and pastiness, flabby musculature, carious infected roots of the teeth, chronic septic tonsillitis, slight enlargement of the heart and increase in the retromanubrial dulness, metallic valvular heart sounds, sinus tachycardia, an aortic systolic murmur, slight periph-

10 DeBoer, S. J. *Physiol* **51** 211, 1917

eral sclerosis and an elevated blood pressure of 180 mm of mercury systolic and 100 mm of mercury diastolic were present

The urine varied in specific gravity from 1 005 to 1 012 and contained from 2 to 30 per cent of moist albumin with hyaline and granular casts. The excretion of phenolsulphonphthalein was from 15 to 40 per cent in two hours. Chemical analyses of the blood revealed nonprotein nitrogen, 36 to 68 mg, cholesterol 132 and 198 mg, and chlorides, from 730 to 760 mg. The blood showed a high grade of secondary anemia and eosinophilia. A heavy infection with *Strongyloides* was present. Nephrosis with a large white kidney was suspected, but operation for bilateral decapsulation revealed small red granular organs. The therapeutic response to diets poor in salt was fairly good, but the response to diuretics, especially methaphen, was spectacular. The patient would leave the hospital only to return with a recurrence. The patient died in uremia.

The diagnosis was chronic nephritis with edema uremia and secondary damage to the heart and vessels.

CASE 5 (numbers 7 and 14 in table 1) —A H P, a white night watchman, aged 65, suffered from paroxysmal attacks of severe nocturnal dyspnea, cardiac asthma, some dyspnea on exertion, pain in the left side of the chest on deep inspiration, weakness, edema of the dependent parts and hemoptysis. The milder symptoms of cardiac failure had been present for two years, but the grave manifestations had been present for only about four months. The patient was obese and hypersthenic, with conspicuous cyanosis of the lips and mucous membranes, telangiectasis, xanthelasma, engorgement of the veins of the neck, enlargement of the heart, an apical systolic murmur, occasional premature contractions, sinus tachycardia, practically unchanged peripheral blood vessels and a blood pressure of 130 systolic and 100 diastolic. Râles were heard at the bases of the lungs, the liver was enlarged, and edema was present in the dependent parts.

The urine varied in specific gravity from 1 015 to 1 022 and contained a trace of albumin and hyaline casts. The excretion of phenolsulphonphthalein was 40 per cent in two hours. The blood chemistry was reported normal, nonprotein nitrogen, 33 mg, uric acid, 3 mg, blood sugar, 152 mg. Roentgenograms taken at a distance of 2 meters showed a cardiac shadow measuring 19.2 cm across and an aortic hemicircle of 5.1 cm. The electrocardiograms showed minute complexes and right and left ventricular ectopic complexes.

The diagnosis was heart failure with edema and congestion of the lungs, liver and kidneys, myocardial insufficiency from a probable adhesive pericarditis.

The patient died, but permission for autopsy was refused.

CASE 6 (number 6 in table 1) —G J, a white lumberjack, aged 38, was troubled with vertigo, headaches, pain in the right flank, bloody urine and occasionally sudden attacks of unconsciousness and blindness, weakness and palpitation. His symptoms had been intermittently present for about eighteen months and had gradually increased in severity and in frequency. Overexertion seemed to be a precipitating factor.

The patient presented a robust appearance. A chronic suppurative otitis media and a chronic sinusitis were present. The heart was enlarged, and the retro-manubrial dulness was increased. The aortic second sound was loudly accentuated. Significant murmurs were not heard. The brachial and radial arteries were slightly, if at all, sclerosed. The blood pressure was as high as 220 systolic and 106 diastolic and averaged 190 systolic and 80 diastolic. The liver was just palpable and was slightly tender, and the kidneys, especially the right, were sensitive to pressure.

The urine showed a specific gravity of 1.016 and contained a heavy trace of albumin, blood and granular and hyaline casts. Ureteral catheterization revealed the right kidney to be the source of the blood. The excretion of phenolsulphonphthalein in two hours was 95 per cent at one test and 25 per cent at one test. The blood chemistry on two occasions was nonprotein nitrogen, 36 and 38, urea nitrogen, 18 and 19, uric acid, 38, calcium, 12 and 14 and blood sugar, 85 and 80 mg. The Wassermann reaction was negative. A secondary anemia was present. The patient improved. The diagnosis was subacute hemorrhagic nephritis.

CASE 7 (number 33 in table 1)—J. H., a negro laborer, aged 66, entered the hospital because of a strangulated right inguinal hernia, and was operated on. Slight edema of the dependent parts, enlargement of the abdomen, oliguria and shortness of breath developed postoperatively, even though the patient remained in bed.

Icterus of the sclerae, moderate anasarca, râles at the bases of the lungs and ascites were the evidences of congestive heart failure with edema. The heart was enlarged, abnormal basal pulsation was noted and the retromanubrial dullness was increased. Sinus tachycardia and aortic diastolic and apical systolic murmurs were heard. The blood pressure was 220 systolic and 100 diastolic.

The urine showed a specific gravity of 1.020 and contained a trace of albumin with many granular and hyaline casts. The phenolsulphonphthalein excretion was 50 per cent at one test and 25 per cent once in the two hour period. The blood chemical analysis showed nonprotein nitrogen, 60 and 40, calcium, 13 and 11, chlorides, 640 and 730 mg, and carbon dioxide, 66 volumes per cent. The Wassermann reaction was negative on two occasions. The blood showed a secondary anemia. The ascitic fluid that was frequently removed had the characteristics of a transudate. The electrocardiograms showed a great left ventricular predominance.

The diagnosis was congestive heart failure with edema and ascites and syphilitic aortic regurgitation.

CASE 8 (number 16 in table 1)—N. B., a Scotch physician and soldier of fortune, aged 70, began to have symptoms of cardiac failure following influenzal pneumonia. In spite of pollakiuria, he began to have swelling of the extremities and abdomen accompanied by dyspnea and nausea. The symptoms continued and increased in spite of adequate therapy.

Besides the symptoms described, a generalized anasarca and a distended abdomen, moderate cyanosis and orthopnea, congestion of the veins of the neck, enlargement of the heart, accentuation of the aortic second sound, no significant murmur, râles at the bases of the lungs, an enlarged and tender liver and ascites were present. The peripheral vessels apparently were not abnormal. The blood pressure was 190 systolic and 122 diastolic.

The urine showed a specific gravity of 1.018 and contained 2 per cent moist albumin, hyaline and fine granular casts, many pus cells and red blood cells. The test for diuresis showed the ability of the kidney to concentrate 1.022, but an inability to secrete much urine. The excretion of phenolsulphonphthalein was 15 per cent. The blood chemistry was reported as follows: nonprotein nitrogen, 54, uric acid, 4, calcium, 15. The icterus index was 10. The direct and indirect van den Bergh tests were positive. Polymorphonuclear leukocytosis was present. The roentgenogram showed an aortic hemicircle of 5.7 cm and a transverse heart measurement of 17.5 cm. The electrocardiograms showed a left ventricular predominance.

The diagnosis was cardiac failure, chronic myocarditis, chronic nephritis and hypertension

CASE 9 (number 13 in table 1)—A G an Acadian farmer, aged 45, came to the hospital because of a chronic cough with expectoration and asthmatic wheezing. His trouble had begun with attacks of bronchitis during the previous five winters. The attacks had become more and more persistent, and shortness of breath and edema of the extremities appeared.

The patient presented the signs of a chronic asthmatic bronchitis, emphysema and sibilant and sonorous râles. The heart was apparently not enlarged; the sounds were distant, the blood pressure was 130 systolic and 90 diastolic; the peripheral vessels were slightly sclerosed. The liver was just palpable and was slightly tender. Slight edema was present in the pretibial tissues.

The specific gravity of the urine was 1.020, it contained a slight trace of albumin and a few hyaline and granular casts. The excretion of phenolsulphonphthalein was 45 per cent in two hours. The blood chemistry revealed a nonprotein nitrogen of 40 mg.

The diagnosis was asthmatic bronchitis, emphysema and chronic nephritis.

CASE 10 (number 23 in table 1)—E J a negress, aged 23, in the sixth month of her first pregnancy, began to vomit, suffer headaches and have convulsions. She had not had any previous symptoms—no urinary disturbance or edema and no known serious infectious disease that might have been an etiologic factor for renal damage.

The eyes were prominent but otherwise not abnormal. Foci of infection were not in evidence in the nose and throat. The heart was not definitely enlarged and nothing significant was observed. The blood pressure ranged from 210 systolic and 140 diastolic down to 190 systolic and 120 diastolic. Dulness in the liver area was diminished, and the uterus was enlarged to the size for a six months pregnancy. Edema was not present.

The urine varied in specific gravity from 1.005 to 1.030 and contained from 10 to 20 per cent moist albumin, red blood cells and hyaline casts. The excretion of phenolsulphonphthalein was 50 per cent in two hours. The blood chemical analysis revealed nonprotein nitrogen 30, uric acid, 4, calcium, 12, chloride 409 mg per hundred cubic centimeters. The Wassermann reaction was negative. Anemia was not present. Electrocardiograms showed sinus tachycardia but did not show predominance. Venesection with the repeated withdrawal of 500 cc of blood, and even the discharge of the fetus did not produce any significant change in the hypertension.

The diagnosis was eclampsia, toxemia of pregnancy, acute hemorrhagic nephritis with gross hematuria and hypertension.

CASE 11 (number 31 in table 1)—W M, an American storekeeper aged 37, had been troubled for a year with pains in the head, the right flank, the perineum and the genitals, with hematuria. The throbbing occipital headache at times became almost unbearable, at such times with vertigo spots appeared before the eyes and the hematuria became most severe. Intermittence was noticed in the severity of symptoms. Some dyspnea on exertion or excitement and nocturia had been noted. The symptoms were aggravated by food. The patient had had four attacks of renal colic in which gravel had been present in the urine from eight to six years before the present illness. Gonorrhea when he was 20, pneumonia in the same year, a questionable lesion on the penis when he was 30 and four stillbirths in the family were considered significant points in the history.

The face was flushed and the eyelids were puffv. The temporal arteries were tortuous and the brachial and radial arteries slightly thickened. The blood pres-

sure was 290 systolic and 190 diastolic, it ranged as low as 220 systolic and 140 diastolic. The heart was slightly enlarged, the apex extending as much as 2 cm outside the midclavicular line, the aortic second sound was ringing, but no murmurs were heard.

The urine showed a specific gravity of 1.018 and contained 1 per cent moist albumin, red blood cells and occasional pus cells. The excretion of phenolsulphonphthalein was 50 per cent in two hours. The blood nonprotein nitrogen was 32 mg and the chlorides, 472 mg. Anemia was not present. The Wassermann reaction was negative.

The diagnosis was hyperpiesia, nephritis (?) and early arteriosclerosis.

CASE 12 (number 22 in table 1)—W. E. G., a white stationary engineer, aged 58, had had headaches, vertigo, positive scotomas, cough, dyspnea, weakness and pollakiuria. The symptoms had caused him to change his occupation to that of night watchman two years before admission. He had known that he had high blood pressure at the age of 48. He had had two attacks of pneumonia and typhoid fever and gonorrhea.

He presented slight pallor, puffiness about the eyes, conspicuous sclerosis of the temporal, brachial, radial and retinal arteries, enlargement of the heart, accentuation of the aortic second sound and a blood pressure of 240 systolic and 135 diastolic.

The specific gravity of the urine varied from 1.010 to 1.015, the urine contained a slight trace of albumin and hyaline and granular casts with occasional red blood cells. The concentration test for diuresis indicated an inability to secrete urine. The excretion of phenolsulphonphthalein was 30 per cent, the nonprotein nitrogen, 45, uric acid, 2, calcium, 13 and blood sugar, 95 mg. The Wassermann reaction was negative. Significant anemia was not present. Electrocardiograms showed left ventricular predominance. The diagnosis was hyperpiesia, arteriosclerosis, chronic myocarditis and chronic nephritis.

CASE 13 (number 11 in table 1)—J. D., a white milk pedler, aged 31, presented himself at the clinic because of swelling of the abdomen and intermittent swelling of the legs, oliguria and diarrhea. He had had measles, mumps, whooping cough and gonorrhea, and had had a chronic addiction to alcohol.

The facies were typically hepatic with spider angiomas in the skin of the face and chest. Icterus of the sclerae, and crowned teeth which showed poor care, were present, the peripheral arteries were not sclerosed, the blood pressure was 110 systolic and 65 diastolic. The heart was displaced upward, with an accentuated pulmonic second sound. The lungs were slightly compressed, the abdomen was distended with ascitic transudate, the liver was enlarged, with superficial venous engorgement, but hemorrhoids were not present. Slight edema was found in the pretibial tissues.

The urine showed a specific gravity of 1.030 and contained urobilin and bile pigments. The stools contained bile. The blood serum contained some pigment. The ascitic transudate was removed, and on the administration of alkali, iodides and merbaphen, the patient improved remarkably.

The diagnosis was alcoholic and, questionably syphilitic, cirrhosis of the liver.

CASE 14 (number 24 in table 1)—S. W., a negress, aged 26, came to the hospital because of swelling of the abdomen and legs, a dry cough, dyspnea, vertigo, nausea, vomiting and nocturia. She was eight months pregnant and had had spontaneous miscarriages and one interrupted pregnancy.

The face was slightly puffy, and the expression was anxious. Some respiratory distress was evident. The heart was at the upper limit of normal in size, and an apical systolic sound, an accentuated pulmonic second sound and a blood pressure

of 204 systolic and 120 diastolic were noted. The abdomen was enlarged by the gravid uterus and a questionable ascites. The extremities were edematous.

The urine showed a specific gravity of 1.014 and contained 2 per cent albumin, hyaline casts and red blood cells. The concentration test for diuresis gave evidence of some difficulty in concentrating. The excretion of phenolsulphonphthalein was 45 per cent. The nonprotein nitrogen was 25 mg and the chlorides, 528 mg. The electrocardiogram showed left ventricular predominance, sinus tachycardia, and changes in the T wave. The Wassermann reaction was variable.

Venesection was of temporary benefit. The delivery of twins gave some relief.

The diagnosis was eclampsia (nephritic) toxemia of pregnancy and myocardial insufficiency (?).

CASE 15 (number 26 in table 1) —C. J., a negro laborer, aged about 60, was admitted to the hospital because of inability to walk. For a year he had been completely disabled with pains in the muscle joints and the girdle region, vertigo, headaches, forgetfulness, difficulty in articulation, incontinence of urine, tremors of the hands and feet, inability to walk, because of falling forward when attempting to do so, and dyspnea and swelling of the feet and legs at times. He had not had venereal disease.

He presented a shuffling gait, staccato speech, fine tremor of the lips, tongue, hands and feet, diminution of the knee reflexes, fixation of the pupils, arcus seniles and well defined peripheral arteriosclerosis. The blood pressure was 150 systolic and 100 diastolic, the heart was enlarged to the left and downward. Slight edema was present in the pretibial tissues.

The urine showed a specific gravity of 1.012 and contained a trace of albumin and a few hyaline casts. The excretion of phenolsulphonphthalein was 40 per cent in two hours. The blood chemistry showed a nonprotein nitrogen value of 37 mg. The Wassermann reaction was negative. Electrocardiograms showed left ventricular preponderance and frequent auricular right and left ventricular ectopic beats and slight tachycardia.

The patient was given six doses of 0.6 Gm of neoarsphenamine followed by a course of mixed treatment. He was discharged with the diagnosis of general arteriosclerosis, chronic myocarditis, arteriosclerotic or syphilitic taboparesis (?).

CASE 16 (number 21 in table 1) —J. B., a white upholsterer, aged 62, suffered from cough and paroxysmal dyspnea at night, which began suddenly six months before examination when he was awakened with the sensation of drowning. The administration of epinephrine relieved him of the attack, but weakness, palpitation and dyspnea on slight exertion became noticeable. Cough, hemoptysis, epistaxis, nocturia, puffiness about the eyes and severe attacks of paroxysmal dyspnea recurred in a month at intervals of three and two weeks and then practically nightly.

Malaria, typhoid fever, dysentery, gonorrhea, buboes and syphilitic infection at 21 years and chronic alcoholism were etiologic factors.

The patient was small and emaciated and presented prominent and tortuous temporal, brachial and radial arteries and pulmonary emphysema with asthmatic bronchitis. Enlargement of the heart, accentuation of the aortic second sound and blood pressures of 210 systolic and 125 diastolic and 180 systolic and 105 diastolic were present.

The urine showed a low specific gravity of 1.010 and contained 4 per cent albumin and many hyaline and coarsely granular casts. The excretion of phenolsulphonphthalein was 50 per cent. The blood chemistry was nonprotein nitrogen, 34, urea nitrogen, 17, uric acid, 3.1, calcium 1.3 and blood sugar, 95 mg. Electro-

cardiograms showed left ventricular preponderance and suggestive evidence of defective intraventricular conduction

The diagnosis was hypertension, advanced arteriosclerosis, chronic nephritis, chronic myocarditis, asthmatic bronchitis, pulmonary emphysema and edema

CASE 17 (number 29 in table 1) —W R, a negro laborer, aged 38, with a history of syphilitic infection, presented symptoms and signs of vascular involvement of the central nervous system, vertigo, headaches, disturbance of speech, weakness in the left arm and both legs with palpitation, enlarged heart, an apical systolic murmur, a ringing aortic second sound, tortuous and thickened brachial and radial arteries and a blood pressure of 260 systolic and 160 diastolic

The urine showed a specific gravity of 1.020 and contained on one occasion a trace of sugar and at other times a trace of albumin and a few pus cells. The excretion of phenolsulphonphthalein was 60 per cent in two hours. The blood chemical analysis showed nonprotein nitrogen, 34 mg, uric acid, 4 mg, calcium, 13 mg and blood sugar, 90 mg. The Wassermann reaction in the blood was strongly positive. The spinal fluid was negative. The roentgenogram taken at a distance of 2 meters showed the transverse diameter of the heart to be 16.1 cm and that of the aortic semicircle to be 5.2 cm. Electrocardiograms gave evidence of left ventricular predominance. Ophthalmoscopic examination revealed silver wire arteries and dilated veins in the fundus.

The diagnosis was hyperpiesia, arteriosclerosis, especially of the cerebral vessels, and relatively little renal impairment.

CASE 18 (number 32 in table 1) —F W, a white farmer, aged 47, noted numbness of the feet for a year, then nocturnal dyspnea, occipital headaches, increasing listlessness and weakness, palpitation and intermittence of heart action and loss of weight.

The patient presented generalized lymphadenitis. The pupillary reactions to light were sluggish. The chest was rachitic, the heart moderately enlarged, the aortic second sound was accentuated and slightly ringing, the brachial and radial arteries were thickened and the retinal arteries small. The blood pressure was 210 systolic and 165 diastolic and 180 systolic and 100 diastolic. Slight edema of the ankles was noted.

The specific gravity of the urine varied in the concentration test between 1.008 and 1.017, and a heavy trace of albumin and finely granular and hyaline casts were found. The excretion of phenolsulphonphthalein was 60 per cent. The blood chemistry studies revealed nonprotein nitrogen, 60, uric acid, 3.5, calcium, 16, blood sugar, 100 and chlorides, 492 mg. The Wassermann reaction was negative. A slight secondary anemia was present. The electrocardiograms showed small complexes and a slight left ventricular predominance.

The diagnosis was hyperpiesia, arteriosclerosis and chronic nephritis.

CASE 19 (number 12 in table 1) —W M, a white pipefitter, aged 33, was admitted to the hospital because of intense persistent jaundice, pruritus and weakness. Four years previously he had been operated on for appendicitis, a year later for adhesions and in another year for gallstones. Four days after the last operation, jaundice appeared and persisted. This was one year previous to admission. A few months later, he became jaundiced. He bled so severely following the extraction of a tooth that transfusion of blood was necessary. The jaundice apparently disappeared spontaneously for a few months after this, only to reappear at the sixth month, associated with enlargement of the liver, pruritus, blurring of vision and loss of weight.

He presented deep jaundice of the sclerae, mucous membranes and skin. The heart was not enlarged, and the vessel walls were soft. The heart rate was 86 a

minute, and the blood pressure was 108 systolic and 70 diastolic. Some abdominal tenderness, an enlarged, smooth liver and an irregular fever were noted.

The specific gravity of the urine was 1.025 and bile, a trace of albumin and epithelial and occasional pus cells were noted. The excretion of phenolsulphonphthalein was 65 per cent in two hours. The blood chemical analyses showed nonprotein nitrogen, 70, calcium, 12, chlorides, 560, blood sugar 90 mg, and carbon dioxide, 74 volume per cent. The Wassermann reaction was negative, the icterus and index was 100 times that of the normal, a slight leukocytosis of 13,500 was present, and bile was absent from the stool.

The diagnosis was complete obstructive jaundice of mechanical origin.

CASE 20 (number 35 in table 1) —F B, a white carpenter, aged 75, was admitted to the hospital for the last time in his fifth attack of generalized edema. He had had dyspnea and cardiac weakness for two and a half years, with congestive failure at intervals and especially after any undue exertion.

Besides general anasarca, he presented orthopnea, cyanosis, engorged veins in the neck, emphysema, great cardiac enlargement, blurring prolongation of the mitral first sound and a distinctly accentuated aortic second sound. The blood pressure was 185 systolic and 135 diastolic, the lungs were emphysematous and moist, the abdomen was tense with ascites, the liver was enlarged, and the extremities were dropsical.

The urine showed a specific gravity of 1.012 and contained a slight trace of albumin with many hyaline and granular casts. The excretion of phenolsulphonphthalein was 17 per cent in two hours. The nonprotein nitrogen was 50, uric acid, 4, calcium, 18 and blood sugar, 90 mg. The electrocardiogram showed complete block of the right bundle branch. The patient died.

The diagnosis was congestive heart failure, chronic myocarditis, chronic nephritis and hypertension.

CASE 21 (number 25 in table 1) —G L, a bartender, aged 59, was brought into the hospital practically comatose with general anasarca. He had been troubled with dyspnea, palpitation and tachycardia, abdominal swelling and oliguria. He had been a chronic drinker of beer.

Besides generalized edema, he presented orthopnea, cyanosis, engorgement of the veins in the neck, an enlarged heart, a systolic murmur, a rapid regular heart rhythm that could be slowed by pressure on the vagus, slight peripheral arteriosclerosis, a blood pressure of 160 systolic and 110 diastolic, questionable enlargement of the liver and ascites.

The urine showed a specific gravity of 1.022 and contained a trace of albumin, a few hyaline casts and red blood cells. The excretion of phenolsulphonphthalein was 25 per cent in two hours. The blood chemistry showed nonprotein nitrogen, 78 and chlorides, 450 mg. The Wassermann reaction was negative. Electrocardiograms showed auricular flutter and, after digitalization, impure flutter and finally fibrillation, which persisted. The patient died of extreme congestive cardiac failure.

The diagnosis was congestive heart failure with general anasarca, chronic myocarditis, chronic nephritis, hypertension, auricular flutter and fibrillation.

CASE 22 (number 27 in table 1) —C W, a negro laborer, aged 42, was admitted because of swelling of the body, headache, some cough and dyspnea. He had had previous attacks of edema, but none as severe as the one which had brought him to the hospital and which had been increasing slowly in severity for several weeks. He had had gonorrhea and a probable syphilitic infection when he was younger.

Besides puffiness of the face, he presented moderate edema of the lower extremities, enlargement of the heart, accentuation of the aortic second sound and a slight aortic systolic murmur, slight sclerosis of the peripheral arteries and a blood pressure of 162 systolic and 92 diastolic

The urine showed a specific gravity of 1.012 and contained 2 per cent albumin, many hyaline and granular casts and an occasional red blood cell. The blood chemical studies revealed nonprotein nitrogen, 82 and chlorides 410 mg. The Wassermann reaction was positive. A mild secondary anemia was present.

The diagnosis was syphilitic aortitis, chronic myocarditis and chronic nephritis with hypertension and edema.

CASE 23 (number T 5 in table 1)—J. K., a white cook on a ship, aged 50, entered the clinic because of edema of the legs and genitals. Previous but less extensive dropsical states had been experienced during the preceding two years, together with increasing dyspnea, orthopnea, weakness, headache, vertigo and persistent cough. A syphilitic infection when he was 30, although he had been treated by injections for seven months, must have been an etiologic factor.

He presented pallor, pastiness, puffy eyelids, cardiac enlargement, accentuated aortic second sound, a pericardial rub, occasional ectopic heart beats, a blood pressure of 225 systolic, 120 diastolic, edema of the lungs, hydrothorax, ascites and anasarca.

The urine varied in specific gravity from 1.010 to 1.020 and in albumin content from 16 to 40 per cent. A few hyaline and coarsely granular casts were present. The excretions of phenolsulphonphthalein were, respectively, 15 per cent, 20 per cent and 40 per cent in two hour periods. Blood chemical studies revealed nonprotein nitrogen, 62 and 50, urea nitrogen, 29, calcium, 2.5, blood sugar, 95 and chlorides, 644. High grade secondary anemia and leukocytosis were present. The electrocardiograms showed left ventricular predominance and changes in the T wave.

At autopsy, the kidneys weighed 240 Gm. each and showed a narrow cortex, injected blood vessels, small cysts, increased connective tissue and casts in the tubules.

The diagnosis was acute exacerbation of a chronic nephritis, hypertension and chronic myocarditis with congestive heart failure.

CASE 24 (number 36 in table 1)—E. B., a white telephone operator, aged 44, had fallen unconscious in his quarters for the third time. He had previously been admitted to the clinic in coma, with paresis and pain in the left arm and leg. Severe headache, dizziness, weakness and numbness and short periods of unconsciousness had been troublesome for years. Dyspnea and precordial pain had been noted for a year. He had had acute nephritis following scarlet fever at the age of 8 and had had hypertension ever since. His father, mother and six sisters had died of disease of the kidneys.

The patient presented nephritic facies with a definite exophthalmos and dilated venules of the skin. Other symptoms included carious teeth, cardiac enlargement, accentuated aortic second sounds, slight arteriosclerosis, a labile hypertension ranging from 270 systolic and 160 diastolic down to 165 systolic and 105 diastolic, emphysematous lungs, amputation of the left foot and slight edema of the extremities.

The urine showed a specific gravity of 1.012 and contained 12 per cent moist albumin and many hyaline and granular casts. The excretion of phenolsulphonphthalein was 5 per cent and 0 per cent in two hours. The blood chemistry studies

revealed nonprotein nitrogen, 95 urea nitrogen, 45, calcium, 4.4 The Wassermann reaction was negative The patient improved on the administration of benzyl succinate.

The diagnosis was chronic nephritis, hypertension and cerebral angiospasm

CASE 25 (number 2 in table 1) —B S, an Acadian fisherman, aged 65, came to the clinic at Charity Hospital because of chronic persistent headache, dizziness, weak spells, shortness of breath and swelling of the feet and legs He had had these symptoms for a year, but there had been a definite increase in the severity of his troubles Palpitation and dyspnea were noted on slight exertion, and occasionally he had paroxysmal attacks of smothering asthma He frequently suffered from nausea, but never vomited He was chronically constipated Urinary frequency every half hour or every hour night and day troubled him considerably His light-headed sensation was extreme at times, and he "fell out" but never lost consciousness The administration of glyceryl trinitrate and amyl nitrite relieved his headache

He presented the usual signs of senility but evidences of discomfort were not seen Arcus senilis was present in each eye The mouth contained a few remaining carious snags, but not any sound teeth The cardiac dulness was definitely increased The aortic and mitral second sounds were loudly accentuated A blowing systolic murmur was heard, and an occasional premature contraction disturbed the rhythm The peripheral blood vessels were definitely sclerosed The blood pressure was 280 systolic, 140 diastolic, but dropped to 260 systolic, 125 diastolic and later to 230 systolic and 120 diastolic, with the administration of apothesine, intrathecally, the drop in blood pressure was from 250 systolic, 140 diastolic to 201 systolic, 110 diastolic in twenty-five minutes The liver was enlarged but not tender Slight edema was present in the pretibial tissues

The urine was clear and acid in reaction, the specific gravity was 1.012, it did not contain albumin or casts The excretion of phenolsulphonphthalein was 20 per cent in two hours The chemical analyses of the blood revealed nonprotein nitrogen, 48 mg per hundred cubic centimeters, urea nitrogen, 12, uric acid, 4.0 and calcium, 12 The Wassermann reactions with the blood and spinal fluid were negative Electrocardiograms showed left ventricular predominance with junctional and auricular ectopic beats

The diagnosis was hyperpiesia arteriosclerosis, chronic myocarditis and chronic nephritis

CASE 26 (number 30 in table 1)) —A S, an American clerk, unmarried, aged 62, came to the hospital because of vomiting and faintness Definite symptoms had not been present until the day before admission, when an attack of nausea, dizziness, faintness and syncope occurred He had had gradual failing of vision and spots before his eyes and severe headaches every morning associated with nausea and occasional vomiting One year before admission, while working, he had a severe attack of vertigo which was followed by a free epistaxis which continued for about eight hours He was relieved of the symptoms for several weeks Within the year before admission, he had had eight or ten attacks of palpitation which came on suddenly and lasted five or ten minutes but did not reappear again for about a month He had had frequency of micturition for many years He had had typhoid fever at 10 years of age acute rheumatic fever at 12 pneumonia at 15 and influenza in 1918

The patient was decrepit His heart was somewhat enlarged The aortic second sound was loud and metallic The sounds at the apex were short and slightly valvular Blood pressure had been as high as 250 systolic 155 diastolic

and as low as 200 systolic, 120 diastolic. The lungs were emphysematous. The abdomen showed conspicuous abdominal breathing and scars in each groin. The radial and brachial arteries were increased in size and were tortuous and thickened. Some edema was present in the pretibial tissues.

The urine showed a specific gravity of 1.010 and contained 1 per cent albumin and many hyaline and granular casts. Blood chemical determinations showed nonprotein nitrogen, 84, urea nitrogen, 50, uric acid, 4, calcium, 3, blood sugar, 90 mg. The blood Wassermann reaction was negative. The blood picture showed a slight secondary anemia.

The diagnosis was hyperpiesia, arteriosclerosis, chronic myocarditis and chronic nephritis.

CASE 27 (number 3 in table 1) —W. H., a white unmarried millwright, aged 59, came to the hospital because of swelling of the feet, ankles and abdomen and shortness of breath. His first symptoms, slight swelling of the abdomen and shortness of breath, were noted seven months previously. After his abdomen began to swell, he noted smothering spells on straining at stool and urination. The edema, especially the puffiness about the eyelids and the swelling of the genitals and even some of the waterlogging of the legs would at first disappear on rest in bed, but gradually the symptoms would not respond to the rest treatment. At times, the dyspnea was so severe that the patient was orthopneic. He had had a sore, which was presumably a syphilitic lesion, at the age of 24. At the age of 48, he took four injections of arsphenamine. He had had frequency of urination, urinating from eight to ten times a day and from five to six times at night. The urine had been smoky at times.

Physical examination revealed a more or less general anasarca, with puffiness of the face as well as the dependent parts. The heart was slightly overactive and distinctly enlarged. A faint systolic murmur was heard at the apex. The aortic second sound was accentuated. The blood pressure which was 180 systolic and 135 diastolic on admission dropped to 165 systolic and 105 diastolic. The rhythm of the heart was made irregular at times by premature contractions. The lungs were emphysematous. The abdomen was enlarged. The fluid waves were evident. The liver was not palpable. The spleen was palpable on deep inspiration.

The urine contained 2 per cent albumin, hyaline and fine and coarse granular casts and a few pus cells. The specific gravity was 1.010 and 1.014. The excretion of phenolsulphonphthalein was 5 per cent in two hours. The blood showed a secondary anemia, a definite retention of nitrogen, nonprotein nitrogen, 90, urea nitrogen, 55, uric acid, 56, calcium, 3.2 mg. The blood Wassermann reaction was negative. The electrocardiogram showed negative T waves in lead I and left ventricular predominance. The patient was given cathartics, and abdominal paracentesis was done with the removal of about 10 liters of fluid on Oct. 20, 1926. On October 25, the edema was subsiding. On October 27, practically all of the edema had disappeared. The patient continued on a salt-free diet, but dyspnea on exertion continued.

The diagnosis was chronic nephritis and hypertension and chronic myocarditis with congestive failure.

CASE 28 (number 28 in table 1) —F. P., a negro farmer, aged 24, was brought to the hospital complaining of swelling of the feet and legs which had been present for ten weeks and which had occurred in two previous attacks in the two preceding winters. Besides edema of the extremities, abdomen and face, he had had dull headache, positive scotomas, abdominal pain and oliguria. In the past he had had pneumonia, gonorrhea and syphilis. For three generations, a total of seven of his relatives had died in a dropsical condition.

He presented generalized anasarca, with puffiness of the face and distention of the abdomen. The retinal arteries were markedly tortuous with widened arterial bands. The peripheral vessels were only slightly thickened. The blood pressure was 185 systolic and 134 diastolic, the heart was enlarged, with an accentuated second sound, but without significant murmurs. Striae were conspicuous over the abdomen, ascites, an enlarged liver, and tenderness were also found.

The specific gravity of the urine varied between 1.005 and 1.010, it contained from 20 to 23 per cent moist albumin, hyaline and granular casts, pus and red blood cells were found. The excretion of phenolsulphonphthalein was 5 and 8 per cent. There were limitations of the concentration test for diuresis in both processes. Blood chemical studies showed nonprotein nitrogen, 99 and 125, uric acid, 4, calcium, 18 and blood sugar, 100 and 95 mg per 100 cc.

The diagnosis was chronic nephritis with edema and hypertension.

At autopsy, the kidneys were pale pink and firm with increased connective tissue and contraction of the cortex. The capsules stripped with difficulty, leaving an irregularly granular surface.

CASE 29 (number 7 in table) —E S, an Italian spinner, aged 20, came to the hospital because of weakness, drowsiness and shortness of breath. He had not worked for several years. Three years before he came to the hospital, his left kidney had been removed for abscess. He had also had his tonsils removed, but he never did recover. In August, 1926, he began to feel weak, and his feet and ankles swelled moderately. Shortness of breath suddenly developed and was noted even when he was quietly walking about. He continued to receive some hypodermic injections from his family physician, but without any improvement. Severe headache, worse at night, developed and remained more or less constant in the frontal region. He had dyspnea, tinnitus and was more or less deaf, once or twice a week, he would have copious epistaxis. He began to lose his appetite and he vomited on three or four occasions. His urine was dark and smoky, and he had a definite fever. He attributed this to a respiratory infection that he had had for about three weeks. He was rarely bothered by nocturia. The patient had had typhoid fever for two months at the age of 11 and influenza in 1918. In 1923, he began to have epistaxis. He felt a bit weak after control of the hemorrhage but did not have other symptoms. In May, 1924, he noticed blood in the urine and pain in the region of the left kidney. The kidney was removed. A month later, he had his tonsils removed because of a possibility of their being a focus of the kidney trouble.

When seen, the patient was propped up in bed and was somewhat drowsy and listless. The skin was pale, sallow and of a somewhat waxy yellowish tint. There was some puffiness over the eyelids. He had a slight exophthalmos and a subconjunctival hemorrhage. His hearing was definitely impaired. The mucous membrane and lips were pale. The heart impulse was well located in the mid-clavicular line in the fifth interspace. Sounds were distinct. Rhythm was regular, the rate being 86 per minute. Murmurs were not heard. The pulmonary second sound was accentuated. The blood pressure was 160 systolic and 90 diastolic. The lungs were normal. The abdomen showed nothing of significance except the scar in the region of the left kidney. The liver and spleen were not palpable. Some edema of the extremities was present.

The urine showed a specific gravity of 1.010 and contained 3 per cent albumin and occasional finely granular casts. The excretion of phenolsulphonphthalein was 0 per cent in two hours. The blood showed a high secondary anemia and slight leukocytosis. The Wassermann reaction was negative. Blood chemical studies

showed nonprotein nitrogen, 100, urea nitrogen, 49, uric acid, 46, calcium, 3.9, blood sugar, 75 mg per hundred cubic centimeters. The patient's uremic coma increased. He had one convulsion on Nov 3, 1926, that lasted five minutes. The pulse rate increased to 108. The temperature fluctuated from subnormal to 99.6. Other phenolsulphonphthalein tests showed complete retention of the dye for two hours. Blood pressure rose to 225 systolic and 80 diastolic, and venesection was done. One hundred and fifty cubic centimeters of blood was removed. Glucose solution was given intravenously but with no avail. The patient died, Nov 4, 1926. Autopsy was refused.

The diagnosis was uremia, chronic nephritis with subacute exacerbation, hypertension and severe secondary anemia.

CASE 30 (BB in table 1)—W. L., a negro section hand, aged 39, came to the clinic complaining of swelling of the legs and abdomen and pain over the heart. His illness dated back only one week, according to his story, although he had had symptoms of cardiac failure for at least six months. He had noted a swelling of the feet after getting wet one week previously, the swelling gradually increased and progressed upward until the abdomen was involved. Shortness of breath, attacks of palpitation, dizziness and cough, with the expectoration of bright red blood, had been symptoms of increasing severity. He had had to get up four and five times each night to urinate. Nausea and some constipation had been present. He had had gonorrhea and inflammatory rheumatism when he was 20, a chancre at the age of 24 and had been treated with intravenous injections of what most likely was arsphenamine. He had also been chronically addicted to alcohol.

The physical examination revealed a general anasarca, a moderately hard edema of the lower extremities and genitals, sluggish pupils and diminished reflexes. The heart was definitely enlarged. A diastolic murmur replaced the aortic second sound and was transmitted to the left border of the sternum, but changed at the apex from its high pitch to a low, rumbling character. The blood pressure was 126 systolic, 38 diastolic. The liver was engorged.

The urine was acid, with a specific gravity of 1.024, a slight trace of albumin and a few red cells, pus cells and granular casts in the sediment. The excretion of phenolsulphonphthalein was 30 per cent.

The diagnosis was chronic nephritis, chronic syphilitic aortic disease with myocardial insufficiency. Autopsy revealed a chronic nephritis and chronic aortic valvulitis.

Autopsy revealed a chronic nephritis and chronic aortic valvulitis.

CASE 31 (number 34 in table 1)—M. P., a colored teamster, aged 32, had suffered for four months with shortness of breath on exertion, epistaxis, irregular, painful vomiting of cloudy fluid, nocturnal vertigo and pollakiuria.

He had had malaria at the age of 10, gonorrhea twice and a chancre at 22, for which he did not receive treatment.

Physical examination at the time of admission revealed that the patient was drowsy and dyspneic, with moderate edema of the ankles and feet and at the bases of both lungs. The inguinal glands were palpable. Retrosternal dulness was increased. The heart was enlarged to the left and downward. A blowing systolic murmur was heard at the apex. The aortic second sound was accentuated. The blood pressure was 190 systolic, 108 diastolic. The liver was felt 6 cm below the costal margin.

The blood Wassermann reaction was strongly positive. The urine showed a specific gravity of from 1.005 to 1.010. Albumin was constantly present in small quantities, and hyaline casts were found on each examination. The blood picture was that of a moderate secondary anemia. The excretion of phenolsulphonphthal-

em was 3 per cent Blood chemical studies showed nonprotein nitrogen, 300, calcium, 7, uric acid, 66, blood sugar, 85 mg

The diagnosis was chronic nephritis, hypertension, chronic syphilitic aortitis and myocarditis with congestive failure

The autopsy revealed small contracted granular kidneys with numerous cystic formations, hypertrophy and dilatation of the heart, aortitis and edema of the lungs

SUMMARY

Analyses were made to determine the distribution of the nonprotein sulphur fractions of the blood in whole blood and in plasma obtained from a series of cases representing various pathologic conditions of the kidneys, heart and liver

The results obtained would seem to indicate that while in normal persons the inorganic sulphate fraction is present only in plasma, in patients with nephritis who show retention of sulphate the inorganic sulphate content of the whole blood rises more rapidly than does the concentration of this fraction in the plasma, indicating diffusion and storage of this constituent in the corpuscles

There does not appear to be any direct relation between the retention of nonprotein nitrogen and inorganic sulphate, or between the latter, the neutral sulphur fraction or the chlorides

THE CARDIOTACHOMETER

AN INSTRUMENT TO COUNT THE TOTALITY OF HEART BEATS
OVER LONG PERIODS OF TIME¹

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From the earliest days of medicine the study of the pulse has been of major interest to physicians, and trained observation of the pulse at the bedside has been of fundamental importance in diagnosis and in treatment. The quality of the pulse gives information about the condition of the heart and arteries, and, in former years, was supposed to reflect specific abnormal bodily states. Up to 100 years ago, the practicing physician paid little attention to pulse rate, but indulged in hair-splitting refinements of classification of pulses of different qualities. Innumerable voluminous but sterile treatises have been published on the quality of the pulse. Quantitative studies of the pulse rate were initiated by Galileo (1620), who synchronized the beat of a pendulum with the pulse and expressed the pulse rate by the length of the pendulum. One hundred years later, Sir John Floyer published a book, called the "Physician's Pulse Watch," in which for the first time careful pulse-numerations are recorded. For this purpose, he employed a watch that ran sixty seconds. It was not, however, until the second quarter of the nineteenth century that counting the pulse was accepted as a routine procedure of importance.¹

The pulse rate, which ordinarily coincides with the heart rate, is not alone a measure of the activity of the heart and so of one important component of its work, but it is also an indicator of the influence that many bodily functions and reactions exert on the heart. The introduction of the sphygmograph, the polygraph and the electrocardiograph have permitted a more intensive and accurate study of these changes in the rates of the heart and pulse, but the nature of these instruments has limited their usefulness in the investigation of this variation in rate. For the efficient operation of these instruments, the patient must be sitting quietly under more or less basal conditions. Recently, Goldschmidt² described an apparatus called the pulse resonator, which is designed to register instantaneous changes of rate over long periods of

¹ From the Medical Division of Montefiore Hospital for Chronic Diseases, New York.

¹ Mitchell, S. W. The Early History of Instrumental Precision in Medicine, *Tr. Cong. Am. Phys. & Surg.* **2**: 179, 1892.

² Kraus, F., Goldschmidt, R., and Seelig, S. Analyse des Pulsrhythmus mit dem Pulsresonator, *Ztschr. f. d. ges. exper. Med.* **53**: 243, 1926.

time The pulse resonator works on the principle of Galileo's pulsilogium A series of pendulums of different periods are acted on by the pulsation of the radial artery, and the pendulum, the period of which corresponds to the pulse rate records electrically on a moving paper This ingenious mechanism is a great improvement over previous ones for this purpose, but, as I shall point out in another communication, it is not altogether accurate Furthermore, the patient must be at rest during the examination

For some years I have been interested in devising an instrument that would register the totality of heart beats over a period of many hours, and that would function accurately while the patient was moving about actively In the development of this instrument, I have been fortunate in having the cooperation of Dr Benjamin Liebowitz, without whose technical knowledge and inventive skill the work would have been impossible

We first attempted to operate a counter by means of an electrical contact, pneumatically actuated by the mechanical impulse of the heart beat or pulse beat We found that this contact required a delicate adjustment, and that unless the patient remained quiet, too many extraneous factors were introduced Muscular movement, coughing and jarring, for instance, would render the count inaccurate We then attempted to pick up the heart beats microphonically, employing first a standard carbon granule microphone and later a telephone receiver the diaphragm of which made direct mechanical contact with the chest by means of a short wooden cylinder cemented to the diaphragm Here, again, it became apparent that if the apparatus were made sufficiently delicate to register accurately every cardiac cycle, it would be necessary to keep the patient quiet, or the sound of his voice, a deep inspiration, or a jar of his body would introduce false registrations

At the suggestion of Prof H B Williams of Columbia University, we then undertook to test the feasibility of utilizing the action current of the heart In our first attempts in this direction we led off the action current of the heart from the hands with the usual electrocardiographic electrodes and passed it through a three-tube, stock resistance coupled amplifier It was possible to operate a sensitive relay and counter with this mechanism, but the apparatus was inadequate, allowing false registrations, as well as missing many heart beats It became evident that the two chief requirements for success were a stable amplifier of large gain and more suitable electrodes At this point, we were fortunate in enlisting the aid of Dr Alfred N Goldsmith, to whom we submitted the problem He and his associate, Mr Julius Weinberger, together with Messrs Theodore A Smith and George Rodwin, worked out the necessary theoretical and practical solution for the amplifier and for some of the accessory apparatus which is described below

DESCRIPTION OF APPARATUS

The method employed consists in picking up the voltage of the action current of the heart with suitable electrodes, amplifying this voltage sufficiently, and passing the amplified current into a relay and counter system. The instrument devised to register the heart beats consists of the following elements: electrodes, amplifier, relay, counter and recorder.

The Electrodes—Two shallow cup-shaped electrodes of monel metal 2.5 cm in diameter and 0.5 cm deep are employed (fig 1). These electrodes are sewed to elastic tapes. The cup is filled with ordinary green soap, which serves as an electrolyte. When the electrodes are applied to the precordium, the tapes are tied around the chest and hold the electrodes in place. In most patients, the electrodes are best placed so that one is in the region of the apex beat and

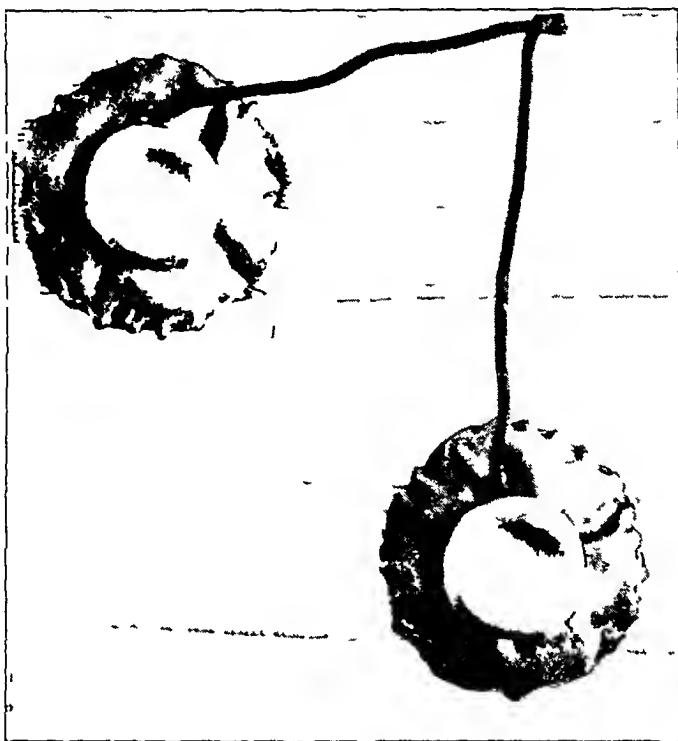


Fig 1—The electrodes are sewed to elastic tape and tied around the chest

the other in the second intercostal space to the right of the sternum. This is approximately the electrical axis of lead II of the electrocardiogram. Wires lead the current from the electrodes to the input terminals of the amplifier.

The Amplifier—The wave form of the action current of the heart is complex, consisting usually of a main peak (the R wave of the electrocardiogram) and several smaller peaks and ripples. The main peak, which is used to operate the mechanism, is of well defined frequency, low in comparison with the acoustic frequencies handled ordinarily in the amplification of the speech, hence, a special type of amplifier is required. Furthermore, it would be desirable to amplify to a less degree the smaller peaks which are of lower frequency and the ripples which are generally of higher frequency. The amplification needed is high, probably of the order of 5,000 to 10,000 in voltage.

The straight resistance coupled amplifier, such as was used in the earlier experiments, has the disadvantage of instability at high gain, in addition, it is expensive and inconvenient. A combination of straight resistance and capacity

coupled circuits with inductance and capacity stages was tried out and was not found entirely satisfactory. When extreme amplification was used, this amplifier could not be made stable. Finally, a four-stage transformer coupled amplifier was designed, special precautions being taken, this arrangement was found stable, and the high amplification required was readily secured.

In order to pass the low frequencies, transformers of high primary impedance were used. To prevent oscillation, condensers of suitable size were placed across the primaries and secondaries of these transformers. These condensers cut the high frequency amplification down to practically zero, but do not influence the amplification of low frequencies to a great extent.

The wiring diagram of the amplifier is shown in figure 2. The overall amplification from input to the plate circuit of the last tube is about 20,000 in voltage at 35 cycles a second. A gain control of the shunt resistance type is placed across the input to the second stage to vary the overall amplification.

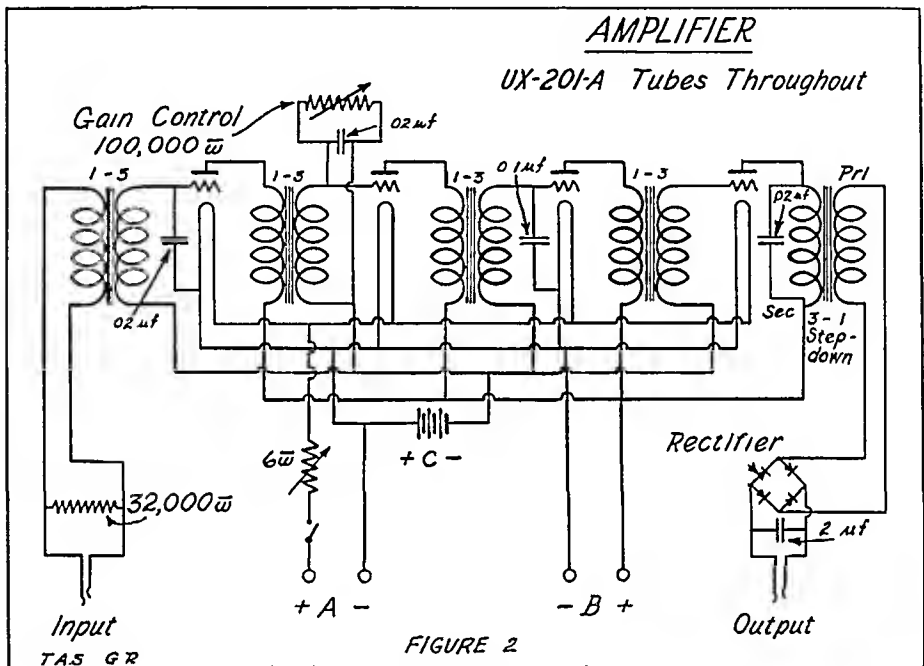


Fig 2—The wiring diagram of the amplifier

Ordinary radio receiving tubes of the UX-201A type are employed with 90 volts B battery and $4\frac{1}{2}$ volts negative C battery. The amplifier is mounted on a spring-suspended subpanel in a copper shielded box. The outside panel contains input and output jacks, starting switch and gain control. Leads coming through the back of the box connect to A and B batteries. The C battery is contained within the box.

The Relays—In the original model a sensitive relay was made to operate by means of the plate current change in the final tube plate circuit. This system required that the constant final stage plate current be biased out of the relay circuit, and hence involved the use of an additional battery and potentiometer. Furthermore, the resistance of the relay was low in comparison with that of the plate circuit. By introducing a step-down transformer between the relay and the plate circuit of the last tube, the additional battery and potentiometer were dispensed with, and higher efficiency was obtained. In the final model of the

apparatus, a full wave copper oxide rectifier was inserted before the relay. This did not require a bias battery and was satisfactory.

The relay is of the Weston model 30 type. A spring contact made of platinum containing 30 per cent iridium 1 inch long, $\frac{1}{16}$ inch wide and 0.004 inches thick was substituted for the fixed contact of the relay. This spring contact aids in minimizing disturbances arising from the smaller peaks and ripples that are passed through the amplifier, and in reducing chatter. The primary relay operates a telegraph relay wound to 150 ohms. On this relay, too, an adjustable

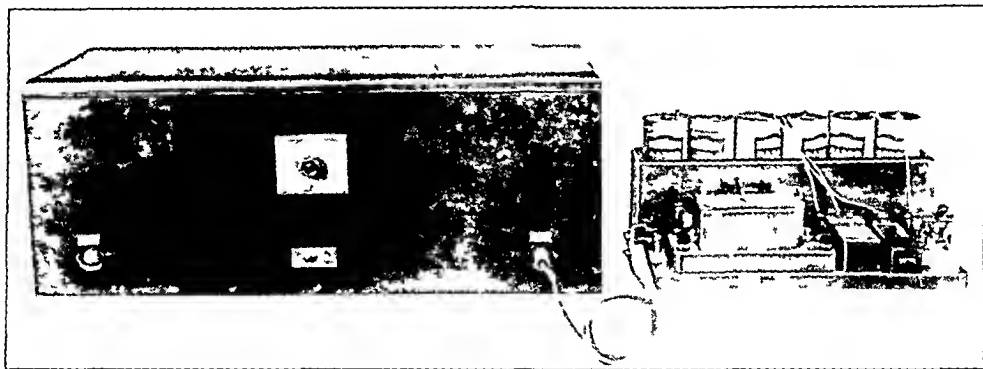


Fig 3—The amplifier, relays and counter

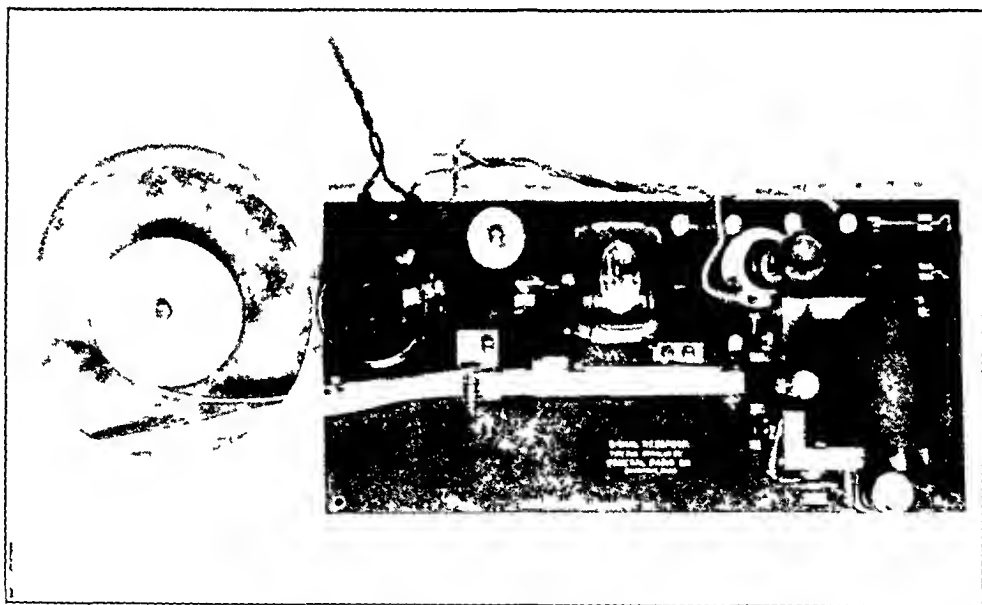


Fig 4—The signal recorder

spring mounted contact was substituted for the fixed contact to avoid rebounding and chatter and consequent false registrations of the counter, and to permit the more rapid action required at high pulse rates.

The Counter—The second relay operates a telephone message counter. This counter was made more rapid in its action by lightening the armature and shortening its excursion. A contact mounted on this counter is closed at the end of each inward excursion of the armature. This closure actuates the recorder.

The Recorder—The recorder is a type 256 Signal Siphon Recorder manufactured by the General Radio Company of Cambridge, Mass (fig 4) The pen records on a moving tape, each stroke of the pen representing one stroke of the counter, or one heart beat With proper adjustment, the recorder will not operate unless the counter armature makes a full stroke

METHOD OF OPERATION

The electrodes are fixed in place over the precordium, one over the apex, the other over the second right intercostal space, the starting switches on the amplifier and the relay are closed, and the gain control on the amplifier is varied until each heart beat is recorded accurately on the counter Too high

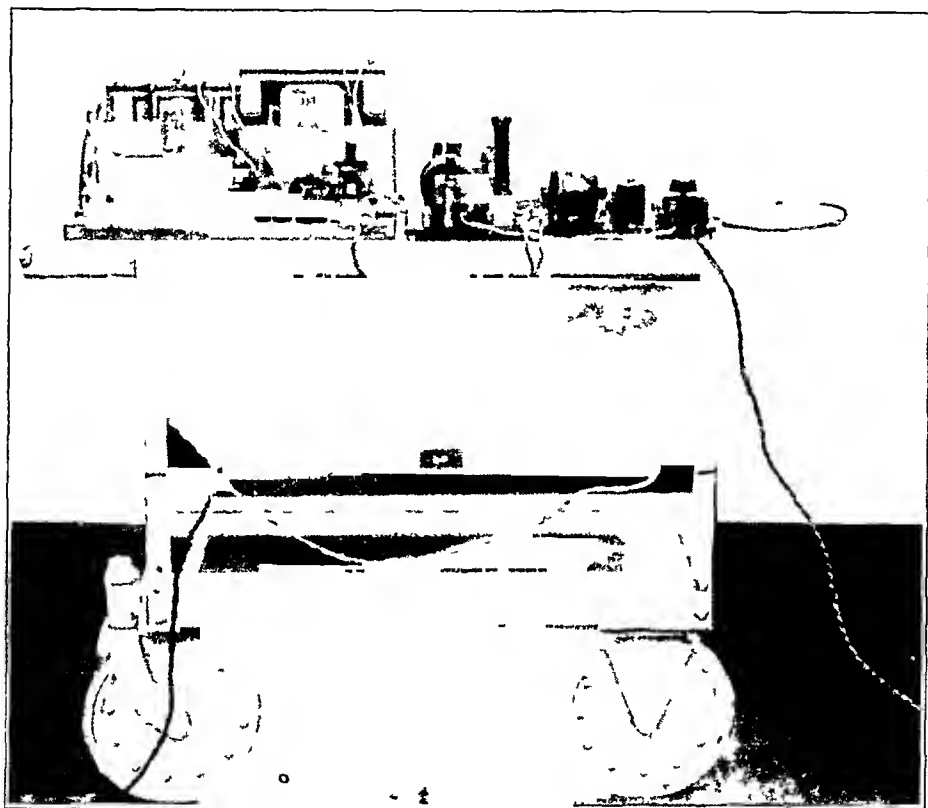


Fig 5—Complete apparatus mounted on a cart

amplification will cause the sensitive relay arm to come up against the stop with such force that it bounds back and makes a double contact, and so registers a false beat on the counter If this occurs, the spring tension of the sensitive relay should be increased, and if this is not sufficient, the gain should be reduced The siphon recorder is then thrown into circuit The number on the counter is read and the time is noted When the observation of the patient is finished, another reading of the counter is made and the time noted In this manner an accurate count of the total number of heart beats in the period elapsed is automatically obtained As a control, the tape of the recorder is inspected, and if it shows no missed or interpolated beats, the count can be accepted as accurate

COMMENT

If the patient holds his hands and fingers immobile, good records can be obtained by the use of immersion jars filled with salt solution as electrodes. Every movement of the hands or fingers, however, causes a large number of disturbances of the relay. German silver electrodes applied to the arms allow more freedom of motion without readily introducing false signals, and flannel bandages soaked in salt solution and held in place on the arms by many turns of wire are still better. With all of these electrodes, however, unguarded movements of the patient lead to false or missed beats. Thus they defeat the primary purpose of the apparatus—to count the heart beats over long periods of time while the subject follows his ordinary activities. These electrical disturbances are probably due to the action currents of the striated muscles, which obscure the registration of the action current of the heart. Moreover, the water evaporates from the bandages that have been moistened with salt solution. These difficulties led to the use of the small chest electrodes and of green soap as an electrolyte. We have used wires up to 20 feet in length between the electrodes and the input jack of the amplifier, thus allowing the patient full activity.

With these electrodes, free motion of the body and extremities does not cause interference with the regular signaling of the action current of the heart. The subjects can indulge in calisthenic exercises, walk, run, sit down on the floor or lie down and roll from side to side without disturbing the regular registration of the counter, as shown by the graphic record. Coughing and laughing do not introduce inaccuracies. However, if the patient makes all of his muscles tense, as in stretching or straining, serious disturbances in the action of the primary relay and in the whole apparatus are introduced. Apparently the electrical currents accompanying these tetanic muscular contractions are sufficiently large and numerous to obscure the action current of the heart. Mobitz,³ in attempting to listen to the amplified action current of the heart by means of a telephone receiver, noted a steadily increasing roaring sound when the subject held his breath, and attributed it to the action currents of the tense respiratory muscles—apparently a similar phenomenon. If insufficient amplification is used, change of position of the patient may interfere with the recording and result in the loss of many heart beats. This is probably due to the changing position of the heart and of its electrical axis. Since the chest electrodes are fixed, an alteration in the electrical axis of the heart may cause such a lowering of the voltage to be led off that it is insufficient to operate the primary relay. To avoid this error, it is necessary to employ the maximum amplification con-

3 Mobitz, W. Ueber Versuche Aktionsströme zu verstärken, *Deutsches Arch f klin Med* **149** 209, 1925

sistent with the regular action of the apparatus and to put the patient through several test exercises before making the final adjustment of amplification gain and of spring tension on the primary relay.

It is essential to insulate the patient during the period of observation, particularly if the floor of the room is a good conductor. We worked in a room with a flooring of magnesite composition and found that whenever the patient, who was placed on a rubber mat, stepped off of the nonconducting rubber, disturbances were apt to arise in the primary relay. The intensity of these disturbances varied from day to day. Similarly, if an uninsulated observer touched the patient, or if the patient touched a radiator or some similar object, the action of the relay became irregular. To insulate the patient, a mat of rubber or other nonconductive material may be placed on the floor. If the patient walks

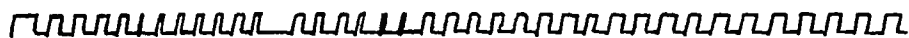


Fig. 6—False beats caused by the uninsulated observer touching the patient



Fig. 7—Record of regular heart beat

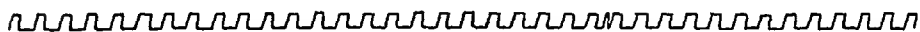


Fig. 8—Extra beat caused by the uninsulated observer touching the patient

around, he should wear rubbers. Similarly, the observer, or the nurse, who must touch the patient's bed, should wear rubbers. If the patient is in bed, the bed should be insulated with rubber castors. Similarly, disturbances may arise if the observer touches the magnet of the siphon recorder. Figure 6 shows extra beats caused by the uninsulated observer touching the patient.

The graphic record on the tape acts as a control of the accuracy of the counter when the heart rhythm is regular. At the end of a period of observation, when the counter reading has been noted, the record on the tape is inspected. If all of the signals follow one another without a break, and if there are no irregularly placed interpolated beats, the count may be accepted as correct. In the record of a long observation totaling several thousand beats, five or ten missed beats may be

disregarded as insignificant. However, it is easy to estimate the number of beats that have not been recorded and to allow for them. Extrasystoles can be recognized when they are followed by a compensatory pause. If the record shows many inaccuracies, the count of that particular run must be disregarded.

We are planning to add time signals to the record on the tape so that changes of rate can be determined at all points on the record.

We have tested the cardiometer on a large series of patients with normal and abnormal hearts under a great variety of conditions, and have been able to obtain satisfactory readings in all of them. The instrument accurately records heart rates from 40 to 200 a minute. The tape runs at a speed of about 12 feet a minute or 72 feet an hour. Although this seems like a long record, its inspection actually takes very little time. In three minutes 72 feet of tape corresponding to one hour's observation can be checked.

Figure 7 is a short strip of the record of case 1. The patient, a girl with simple tachycardia, was under test for forty minutes. During that time, her heart beat 4,740 times, which represents an average rate of 118.5 a minute. The graphic record shows accuracy of the counter with two exceptions, both alike. One of these is shown in figure 8 where an extra interpolated beat was evident. This was caused by the observer touching the patient and was noted at the time it happened. The detailed observations of case 1 are given in table 1. Figure 9 is the record of a patient with mitral stenosis, whose rate was 104 at rest and rose to 200 while she was running in circuit with the cardiometer. The record which is continuous and which should be read from left to right and from above downward, shows the absolute accuracy of registration. Figure 10 shows simultaneous cardiograms and tracings of the cardiometer of a patient with auricular fibrillation and a heart rate of 118. The records are of different lengths because of the different speed of the two papers. The two tracings correspond absolutely not alone in the total number of beats, but in their relative spacing as well. Figure 11 is a similar tracing of another patient with auricular fibrillation, with a rate of 69. A pulse tracing is substituted for the cardiogram and shows similar correspondence with the cardiometer.

Table 1 represents observations on three patients. The sample rate is a casual fifteen second count taken with a watch. The effect of eating is well shown in case 2, a woman with auricular fibrillation. The rate rose from 97 to 124. Case 3 is a record of a girl with mitral stenosis and simple tachycardia. The observations were taken in the evening with the patient in bed.

The possible clinical applications of the cardiometer are manifold. Many physiologic problems, such as the response of the heart

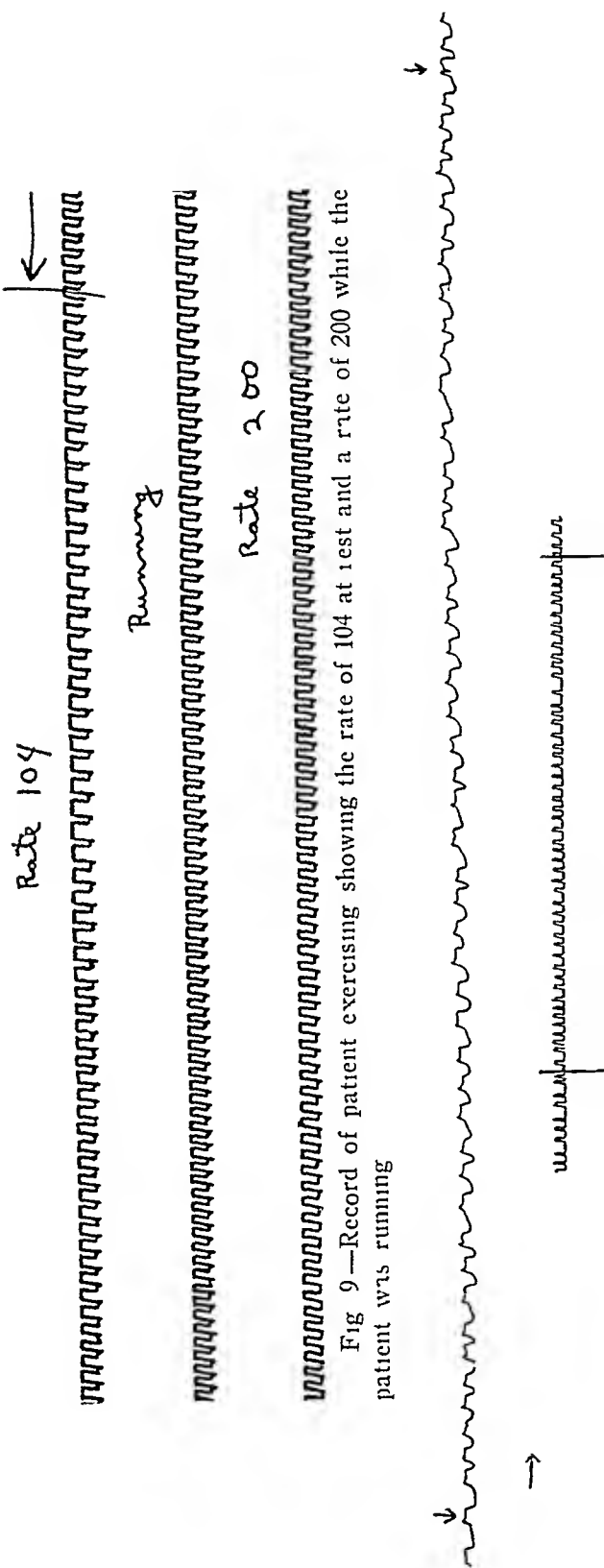
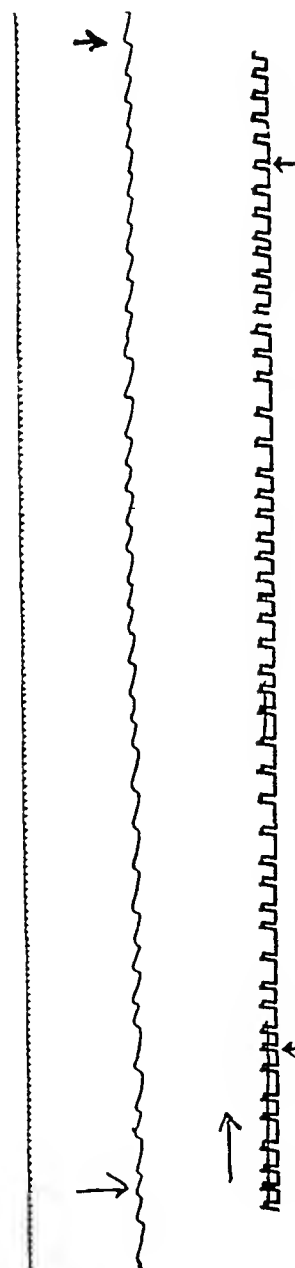


Fig 10—Simultaneous cardiogram and cardiograph tracing, auricular fibrillation



to exercise, drugs, and other stimuli can be studied. The response of the heart during exercise can be accurately measured. As an accessory in many physiologic and clinical examinations, such as basal metabolic rate and minute volume flow determinations, it is invaluable.

Record of Heart Beat in Three Patients

| (Read up the columns) | | | | | | |
|-----------------------|---------|------------------|-------------|-----------|-------------|-----------------------------|
| | Time | Counter Readings | Total Beats | True Rate | Sample Rate | Remarks |
| Case 1 | 11 42 | 11,999 | | | | |
| | | | 686 | 98 | | |
| | 11 35 | 11,313 | | | | |
| | | | 1,275 | 127.5 | | |
| | 11 25 | 10,038 | | | 128 | Half sitting in wheel chair |
| | 11 19 | 9,321 | | | 114 | Lying in wheel chair |
| | | | 837 | 119.6 | | |
| | 11 12 | 8,484 | | | 128 | |
| | | | 1,225 | 122.5 | | |
| | 11 02 | 7,259 | | | 120 | Sitting in wheel chair |
| Total | 40 min | | 4,740 | 118.5 | | |
| Case 2 | 12 26 | 8,473 | | | 109 | Sitting quietly |
| | | | 783 | 97 | | |
| | 12 18 | 7,690 | | | 119 | Finished dinner |
| | | | 904 | 124.2 | | |
| | 12 10 | 6,696 | | | 112 | Began dinner |
| | | | 683 | 97.9 | | |
| | 12 03 | 6,013 | | | 101 | |
| | | | 2,547 | 94.3 | | |
| | 11 36 | 3,466 | | | 90 | Sitting quietly |
| Total | 50 min | | 5,007 | 100.1 | | |
| Case 3 | 11 35 | 19,683 | | | 108 | Awake |
| | | | 1,926 | 96.3 | | |
| | 11 15 | 17,757 | | | 100 | Dozing |
| | | | 1,958 | 97.9 | | |
| | 10 55 | 15,799 | | | 96 | Sleeping |
| | | | 1,970 | 98.5 | | |
| | 10 35 | 13,829 | | | 108 | Dozing |
| | | | 2,156 | 107.8 | 112 | Awake, 10 22 |
| | 10 15 | 11,673 | | | 112 | Sleeping |
| | | | 2,113 | 105.6 | | |
| | 9 55 | 9,560 | | | 112 | Sleeping |
| | | | 2,151 | 107.5 | | |
| | 9 35 | 7,409 | | | 106 | Trying to sleep |
| | | | 2,111 | 105.5 | | |
| | 9 15 | 5,298 | | | 108 | Trying to sleep |
| | | | 2,222 | 111.1 | | |
| | 8 55 | 3,076 | | | 106 | Reading in bed |
| | | | 2,276 | 113.8 | | |
| | 8 35 | 800 | | | | |
| Total | 3 hours | | 18,883 | 104.9 | | |

able. The cardi tachometer will give us for the first time an actual count of the total number of heart beats under the conditions and activities of every day life. The device will be of particular value in determining the clinical significance of the simple tachycardias. It is often difficult to ascertain whether a tachycardia is persistent or only transient and due to an anxiety neurosis or to the excitement of the

examination The cardi tachometer, particularly if it is run while the patient is asleep, will readily distinguish the persistent rapid heart rate that occurs in cases of myocarditis or exophthalmic goiter from a functional acceleration

SUMMARY

An instrument which has been named the "cardiotachometer" is described, which is actuated by the action current of the heart and records automatically the totality of heart beats over long periods of time

PLASMA AND CORPUSCULAR CHLORIDES IN PEPTIC ULCER *

LEON BLOCH, M D

AND

A M SERBY, M D

CHICAGO

The work on which this paper is based was done for the purpose of determining whether in cases of peptic ulcer there is a possible relationship between the amount of various chloride constituents of the blood and the amount of free hydrochloric acid secreted in a stated interval at different stages of which blood was withdrawn for examination. While such a relationship was difficult, if not impossible, to discover, other facts of interest and questions arose which it was felt might be of sufficient interest to report.

That there is an increase in both free and total acidity and in the amount of gastric secretion is well known. The results of studies on the blood chlorides in these cases are not so well known, principally because of the small number of studies on this subject. Jordan¹ states that in forty-one cases of ulcer, the average level of whole blood chlorides after treatment was 570 mg per hundred cubic centimeters of blood and in ten normal cases 593 mg. Arnold² found that on a salt poor, meat-free diet there is a tendency for the serum chloride to increase as long as the diet is maintained. Molnar and Hetenyi³ found that in conditions of hyperacidity the chloride content of the cells and plasma are below normal. We attempted to answer the question whether there is a fundamental difference between normal persons and those with peptic ulcer, by a study of the chloride content of the whole blood, plasma and corpuscles in twenty cases of ulcer in which the diagnosis was made by clinical and roentgenologic methods and

*From the Stomach Study Group and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital, and the Nelson Morris Institute for Medical Research.

¹ Beds were available for this work through a grant by Mr Julius Rosenwald.

1 Jordan, Sara M. Calcium Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalies, *J A M A* **87** 1906 (Dec 4) 1926.

2 Arnoldi, Walter. Der prozentuale Chlorgehalt des Blutserums bei kochsalzarmer und kochsalzreicher fleischfreier Ernährung sowie bei verschiedener Flüssigkeitszufuhr, *Berl klin Wchnschr* **50** 675, 1913.

3 Molnar, B, Jr, and Hetenyi, G. Ueber den Chlorgehalt des Blutserums bei Sekretionsstörungen des Magens und Beeinflussung der Anazidität durch Kochsalz, *Arch f Verdaunngskr* **30** 8, 1922.

in some cases confirmed by operation. Thirteen patients were studied within forty-eight hours after they were admitted to the hospital and before any treatment was given and seven were studied at various periods after treatment was instituted.

METHOD

Ten cubic centimeters of oxalated blood was centrifugalized for ten minutes immediately after it was taken, and the plasma was withdrawn. The chlorides were estimated by the Whitehorn⁴ method and recorded in milligrams per hundred cubic centimeters of plasma, whole blood or corpuscles. The corpuscular chloride content was calculated from that of the whole blood and blood plasma. At the end of two weeks similar determinations of the chlorides were made at the start,

TABLE 1—*Results Attained in the Determinations of the Chlorides Before Treatment*

| Case | Whole Blood | | | Plasma | | | Corpuscle | | |
|---------|-------------|--------|---------|--------|--------|---------|-----------|--------|---------|
| | 0 Min | 75 Min | 150 Min | 0 Min | 75 Min | 150 Min | 0 Min | 75 Min | 150 Min |
| 1 | 471.9 | 442.2 | | 559.4 | 561.0 | | 377.1 | 313.5 | |
| 2 | 455.4 | 438.9 | | 577.5 | 554.4 | | 323.1 | 313.8 | |
| 10 | 430.6 | 412.5 | | 548.0 | 529.6 | | 308.8 | 285.6 | |
| 11 | 503.3 | 513.2 | | 589.1 | 597.3 | | 410.4 | 422.1 | |
| 12 | 564.9 | 510.8 | 476.4 | 621.5 | 624.2 | 615.5 | 503.5 | 346.4 | 325.8 |
| 15 | 486.6 | 435.6 | 442.2 | 580.4 | 595.7 | 595.7 | 285.0 | 262.1 | 275.8 |
| 16 | 405.9 | 397.6 | 420.7 | 580.8 | 575.9 | 589.1 | 212.3 | 204.4 | 233.3 |
| 17 | 438.9 | 445.5 | 445.5 | 599.0 | 602.3 | 602.3 | 265.4 | 275.6 | 275.6 |
| 18 | 410.8 | 393.0 | 400.9 | 599.0 | 544.0 | 590.7 | 206.9 | 235.6 | 195.2 |
| 19 | 455.4 | 463.6 | 466.9 | 617.1 | 618.9 | 612.2 | 280.2 | 295.4 | 309.6 |
| 20 | 438.9 | 455.4 | 453.7 | 590.7 | 608.9 | 605.6 | 274.4 | 294.0 | 288.1 |
| 21 | 438.9 | 427.3 | | 599.0 | 589.0 | | 265.4 | 252.1 | |
| 22 | 450.4 | 460.3 | 457.0 | 603.9 | 610.5 | 608.9 | 284.2 | 297.5 | 292.5 |
| Average | 457.9 | 446.0 | 445.4 | 589.3 | 585.1 | 602.7 | 315.2 | 292.1 | 275.1 |

seventy-five minutes and one hundred and fifty minutes after the start of a two and one-half hour period during which fractional tests were made at one-half hour intervals to determine the free and total gastric acidity. The figures of Dodds and Smith⁵ in ten normal cases were taken as a standard of comparison in this report. The tables give the results attained in thirteen cases before treatment was begun (table 1), the results when the determinations were made after treatment only (table 2), and when they were made before and after treatment was started (table 3). Table 4 is a statement of the figures of ten normal cases, and table 5 shows the wide variations in individual instances. It can thus be seen from table 5, that the differences in the chloride content before and after treatment are negligible when compared to the

⁴ Whitehorn, J. C. Method for Determination of Blood Chlorides, *J. Biol. Chem.* 45:449, 1921.

⁵ Dodds, E. C., and Smith, K. S. Variations in the Blood Chlorides in Relation to Meals. *J. Physiol.* 58:157 (Dec. 28) 1923.

TABLE 2—Results Attained in the Determinations of the Chlorides After Treatment

| Case | Whole Blood | | Plasma | | Corpuscle | |
|------|-------------|------------|--------|------------|-----------|------------|
| | Before | 75 Minutes | Before | 75 Minutes | Before | 75 Minutes |
| 3 | 433.9 | 429.0 | 541.0 | 542.9 | 317.9 | 305.6 |
| 4 | 603.9 | 607.2 | 562.7 | 557.7 | 648.8 | 660.8 |
| 5 | 389.4 | 417.4 | 534.6 | 552.6 | 232.1 | 270.6 |
| 6 | 521.4 | 528.0 | 618.8 | 612.2 | 417.9 | 436.9 |
| 7 | 442.2 | 442.2 | 572.6 | 567.6 | 300.8 | 306.3 |
| 8 | 569.3 | 572.6 | 686.4 | 671.6 | 442.5 | 465.4 |
| 9 | 488.4 | 501.9 | 622.1 | 600.1 | 343.5 | 401.7 |

TABLE 3—Results Attained in the Determinations of the Chlorides Before and After Treatment

| Case | Whole Blood | | | Plasma | | | Corpuscle | | |
|-------------|-------------|--------|---------|--------|--------|---------|-----------|--------|---------|
| | 0 Min | 75 Min | 150 Min | 0 Min | 75 Min | 150 Min | 0 Min | 75 Min | 150 Min |
| 15 | 486.6 | 435.6 | 442.2 | 580.4 | 595.7 | 595.7 | 385.0 | 262.1 | 275.8 |
| 15 repeated | 438.9 | 427.3 | 430.6 | 595.7 | 570.9 | 599.0 | 269.0 | 270.8 | 246.0 |
| 16 | 405.9 | 397.6 | 420.7 | 580.8 | 575.9 | 589.1 | 212.3 | 204.4 | 238.3 |
| 16 repeated | 430.6 | 429.0 | 437.2 | 605.6 | 602.3 | 605.6 | 241.0 | 241.2 | 234.8 |
| 17 | 138.9 | 445.5 | 445.5 | 599.0 | 602.3 | 602.3 | 265.4 | 275.6 | 275.6 |
| 17 repeated | 453.7 | 421.2 | 442.2 | 610.5 | 579.6 | 612.2 | 283.8 | 249.6 | 238.1 |
| 18 | 410.8 | 396.0 | 400.9 | 599.0 | 544.0 | 590.7 | 206.9 | 235.6 | 195.2 |
| 18 repeated | 442.2 | 443.8 | 438.9 | 592.4 | 605.6 | 599.0 | 279.6 | 268.5 | 265.5 |
| 20 | 438.9 | 455.4 | 453.7 | 590.7 | 603.9 | 605.6 | 271.4 | 291.0 | 288.1 |
| 20 repeated | 430.6 | 438.9 | 453.7 | 570.9 | 590.0 | 590.0 | 278.6 | 265.5 | 296.3 |
| 21 | 498.9 | 427.3 | | 599.0 | 589.0 | | 265.4 | 252.1 | |
| 21 repeated | 453.7 | 445.5 | 463.6 | 582.5 | 608.9 | 605.6 | 314.2 | 268.5 | 308.7 |

TABLE 4—Chloride Content of Whole Blood, of Plasma and of Corpuscles in Normal Persons*

| | Sodium Chloride in Mg per 100 Ce | | |
|---------|----------------------------------|--------|-----------|
| | Whole Blood | Plasma | Corpuscle |
| 1 | 480 | 605 | 345 |
| 2 | 560 | 650 | 463 |
| 3 | 485 | 570 | 393 |
| 4 | 500 | 785 | 191 |
| 5 | 480 | 610 | 339 |
| 6 | 420 | 570 | 252 |
| 7 | 440 | 580 | 288 |
| 8 | 475 | 570 | 372 |
| 9 | 490 | 590 | 382 |
| 10 | 440 | 585 | 305 |
| Average | 477 | 609 | 333 |

* In the whole blood the figures vary from 420 to 560, in plasma from 565 to 785 and in corpuscles from 191 to 463.

TABLE 5—Chloride Content of Whole Blood, of Plasma and of Corpuscles Before and After Treatment

| | 0 Min | 75 Min | 150 Min |
|---|-------|--------|---------|
| Average of chloride content of whole blood before treatment | 458 | 416 | 445 |
| Average of chloride content of whole blood after treatment | 469 | 469 | 414 |
| Average of chloride content of plasma before treatment | 589 | 585 | 603 |
| Average of chloride content of plasma after treatment | 592 | 590 | 604 |
| Average of chloride content of corpuscles before treatment | 315 | 292 | 275 |
| Average of chloride content of corpuscles after treatment | 336 | 339 | 272 |

individual variations and inconclusive in showing the effect of treatment on the chloride content of the blood constituents. The study of the gastric acidities in these cases failed to show any constant relationship between the chloride content and the acidity curves.

It is interesting to note that the plasma chloride attains the highest level and shows the smallest variations, the corpuscular chloride the lowest level and the largest variations and the whole blood figures in between the other two.

The question arises as to whether alkali treatment produces a disturbance in the chloride reservoir, if such reservoir exists. If there is any change, it is to be found in the tendency of the corpuscular chloride content to increase after treatment. It is interesting to note that in the cases in which a simultaneous study of the gastric juice was made during the periods in which the blood studies were made, the changes, when definitely apparent, occurred in the corpuscles. The corpuscles generally showed a decrease in chlorides at the beginning of the fractional test meal and a return to normal after seventy-five minutes.

The following points are of interest in chloride metabolism.

1 Are the corpuscles the principal chloride carriers? They appear to be, but this cannot be definitely proved.

2 Do the corpuscles supply chlorides as needed and act as a chloride reservoir for the plasma? They appear to do this because of a greater constancy in chloride content of the plasma over the corpuscles and the variability of the chlorides of the corpuscles.

3 Is there some source of supply for the restoration of chlorides? The chloride content of the food intake is low on the diet allowed in the cases cited.

Why should the chloride content remain high and in some instances be higher after treatment? Lim and Ni⁶ carried out studies on the blood chloride in animals with a Pawlow pouch and found a diminution in the blood chlorides. Their results, however, are not to be compared with those in human beings, because the constant withdrawal of all the gastric secretion as it accumulated prevented the absorption of any of the chlorides from the gastric juice, whereas in man the secretion is retained. This raises further questions.

4 Do the alkali ions of the alkali administered in any way help to bind chlorides and thereby help to maintain a higher chloride content after treatment than before? At present no attempt is made to answer this question.

5 Does the corpuscular chloride represent more truly the changes that occur in the whole blood? From the fact that the greatest variations occur in the corpuscles, this would appear to be true. However, this is only a conjecture and more experimental work is required to prove or disprove this.

⁶ Lim, R. K. S., and Ni, T. S. Changes in Blood Constituents Accompanying Gastric Secretion. I. Chlorides, *Am J Physiol* **75** 475 (Jan) 1926.

CONCLUSIONS

- 1 The results obtained in normal persons and in patients with peptic ulcer do not show great differences
- 2 The plasma chloride content reaches the highest level and shows the smallest variations
- 3 The corpuscular content attains the lowest level and is less constant
- 4 The changes in the corpuscular content suggest that the corpuscles are important in chloride metabolism
- 5 No close relationship between the blood chlorides and the gastric acidity is noticed

EFFECT OF TOXEMIA ON TOLERANCE FOR DEXTROSE AND ON THE ACTION OF INSULIN *

J SHIRLEY SWEENEY, M D

DALLAS, TEXAS

In a previous communication, I¹ presented data showing the effect of toxemia on the tolerance for dextrose of rabbits intoxicated with diphtheria toxin. Daily tests for tolerance for dextrose were made on the animals during the course of their toxemia, and a progressive decrease in the tolerance for sugar was noted.

The series of observation to be presented in this article were made on rabbits that were treated as described and, in addition, they received uniform doses of insulin each time dextrose was administered. It was thought that by this procedure some analytic information might be obtained as to the effects of toxemia on the tolerance for dextrose and on the action of insulin.

Four rabbits were used, one as a control. All food was withdrawn from the cages, but water was allowed, and a single injection of 0.0075 cc of diphtheria toxin² was given subcutaneously to each animal except the control. On the following day, or twenty-four hours later, tests of the tolerance for dextrose were begun and were made daily on each animal until its death. Five grams of dextrose in 25 cc of water was given by stomach tube. Two units of insulin² were given daily, fifteen minutes after the administration of the dextrose. Samples of blood for determination of the sugar content were drawn from the marginal veins of the ear before the administration of dextrose and thirty, sixty and one hundred and twenty minutes following its administration. All of these determinations were made according to the Folin-Wu method. Of the three toxic animals, one lived six days, one seven and the third eight days. The control animal was fed at the conclusion of the experiment and did not show any untoward effects of the starvation.

The results of the daily tests are tabulated in tables 1, 2, 3 and 4 and are presented graphically in charts 1, 2, 3 and 4.

There is one outstanding observation in these experiments. Examination of the curves shows that the two units of insulin given each day,

* From the Departments of Internal Medicine and Physiology, Baylor University, College of Medicine.

1 Sweeney, J S, and Lackey, R W. The Effect of Toxemia on Tolerance for Dextrose, Arch Int Med **41** 257 (Feb) 1928.

2 I am indebted to the Eli Lilly Company, who kindly supplied the diphtheria toxin and insulin used in this experiment.

fifteen minutes after the administration of the dextrose, had a persistent and fairly uniform action in lowering the postprandial blood sugars in the presence of an increasing toxemia. It will be noted that the two hour determinations in two or three instances were not materially lower than the one hour readings. In one instance there was an actual rise at the two hour interval, but this increase was slight. I¹ have recently shown that daily tests to ascertain the tolerance for dextrose of rabbits that were made toxic with diphtheria toxin, but that did not receive insulin, showed that there was an increasing inability to remove

TABLE 1—*Results of Daily Tests of Tolerance of Rabbit 4 for Dextrose*

| Hours of Fasting and Toxemia | Temperature (F) Rectal | Blood Sugar, Mg per 100 Cc | | | |
|---------------------------------|------------------------------|----------------------------|----------------|------------|-------------|
| | | Fasting | After Dextrose | | |
| | | | 30 Minutes | 60 Minutes | 120 Minutes |
| 24 | 104.3 | 114 | 179 | 171 | 114 |
| 48 | 104.1 | 115 | 169 | 189 | 157 |
| 72 | 103.2 | 118 | 182 | 244 | 198 |
| 96 | 103 | 118 | 200 | 217 | 163 |
| 120 | 102.8 | 123 | 241 | 282 | 233 |
| 144 | 103 | 154 | 259 | 303 | 303 |
| 168 | 102.8 | 145 | 278 | 278 | 260 |
| 192 | | 154 | 339 | 400 | 400 |

* The animal received 0.0075 cc of diphtheria toxin. Two units of insulin were given subcutaneously each day fifteen minutes after the administration of dextrose.

TABLE 2—*Results of Daily Tests of Tolerance of Rabbit 5 for Dextrose*

| Hours of Fasting and Toxemia | Temperature (F) Rectal | Blood Sugar, Mg per 100 Cc | | | |
|---------------------------------|------------------------------|----------------------------|----------------|------------|-------------|
| | | Fasting | After Dextrose | | |
| | | | 30 Minutes | 60 Minutes | 120 Minutes |
| 24 | 104.5 | 114 | 187 | 177 | 112 |
| 48 | 102.8 | 131 | 200 | 198 | 168 |
| 72 | 102.1 | 110 | 183 | 236 | 244 |
| 96 | 102.5 | 95 | 189 | 233 | 222 |
| 120 | 101.9 | 139 | 241 | 308 | 308 |
| 144 | 102.8 | 154 | 286 | 364 | 377 |
| 168 | 103.4 | 139 | 278 | 323 | 308 |

* The animal received 0.0075 cc of diphtheria toxin. Two units of insulin were given subcutaneously each day fifteen minutes after the administration of dextrose.

dextrose from the blood. In fact, there appeared to be a quantitative relationship between the intensity of the toxemia and the impairment of the rabbits' tolerance for sugar. With these observations in mind, it requires only casual inspection of the charts accompanying this article to see that the toxemia does not cause an appreciable change in the action of the injected insulin, in other words, as stated before, there seems to have been a consistent "two unit action" throughout these experiments, even in the presence of an increasing toxemia.

COMMENT

In order to suggest an explanation for the phenomenon described and other related phenomena of the effect of toxemias on the tolerance

for dextrose, it is necessary to consider the factors involved in the production of the so-called normal tolerance curve. I³ have previously suggested that the ingestion of dextrose stimulates the production of sufficient insulin to cause the disappearance of the excess blood sugar within two or three hours. This effect of the ingested dextrose has been suggested by others.⁴ Jordan⁵ has more recently presented some experimental work that supports this view. It was further suggested that the

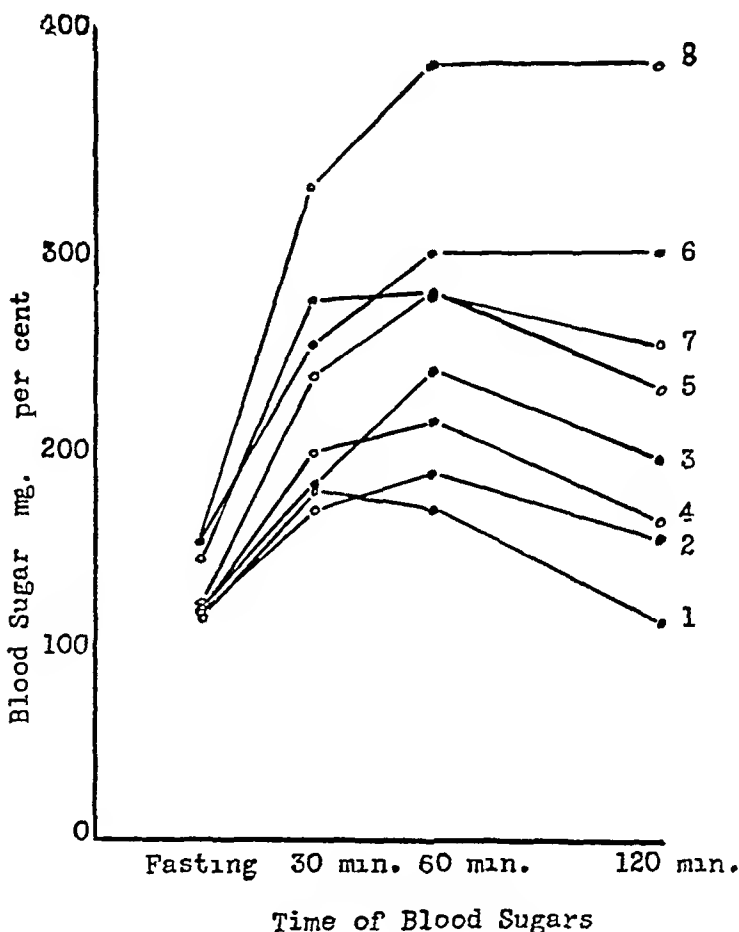


Chart 1—Daily curves showing tolerance of rabbit 4 for dextrose. The animal received 0.0075 cc of diphtheria toxin. Two units of insulin were given subcutaneously each day fifteen minutes after the administration of dextrose. The figures at the end of each curve represent the number of days of fasting and toxemia.

3 Sweeney, J. S. Dietary Factors That Influence the Dextrose Tolerance Test, *Arch Int Med* 40 818 (Dec) 1927.

4 Sevringhaus, E. L., and Smith, M. E. *Science* 61 92, 1925. Thalhimer, W. F., Raine, Forrester, Perry, M. C., and Buttles, J. The Effect of Injections of Dextrose and of Insulin and Dextrose Upon Blood Sugar, *J. A. M. A.* 87 391 (Aug 7) 1926. Lawrence, R. D. *Quart J Med* 20 77, 1926.

5 Jordan, E. M. *Am J Physiol* 80 441, 1927.

excess of blood sugar was largely stored as glycogen. This hypothesis is consistent with the more recent views regarding the mode of action of insulin⁶. I am familiar with the somewhat discordant experimental results bearing on this subject. For a more comprehensive analysis of this phase of the subject, the reader is referred to the excellent discussion of Barbour, Chaikoff, Macleod and Orr⁶ on their experimental results.

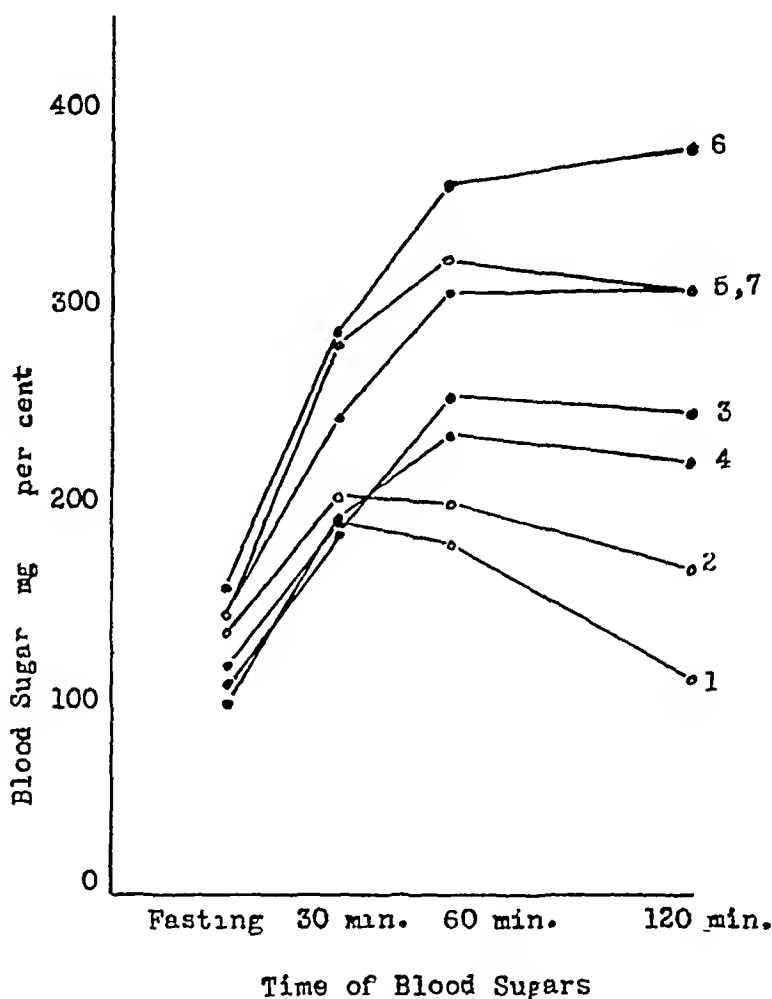


Chart 2—Daily curves showing tolerance of rabbit 5 for dextrose. The animal received 0.0075 cc of diphtheria toxin. Two units of insulin were given subcutaneously each day fifteen minutes after the administration of dextrose. The figures at the end of each curve represent the number of days of fasting and toxemia.

I³ have previously demonstrated that persons who have been fed on rich carbohydrate diets for two days prior to the performance of a test of their tolerance for dextrose have shown a marked increase in

⁶ Rabinowitch, I. M., and Bozin, Eleanor V. *Brit J Exper Path* 8 4, 1927.
 Barbour, A. D., Chaikoff, I. L., Macleod, J. J. R., and Orr, M. D., *Am J Physiol* 80 243, 1927.
 Macleod, J. J. R. *Physiology and Biochemistry in Modern Medicine*, 5, St. Louis, C. V. Mosby Company, 1926.

tolerance Persons who have been starved or who have been fed on exclusive fat or protein diets have shown a definitely decreased tolerance for dextrose The effect of diet and fasting on tolerance for carbohydrates has been referred to by other investigators⁷ To explain these results, I have suggested that there was a more active stimulation of the production of insulin in those who had received carbohydrate feedings which resulted in a quick removal of the excess dextrose from the blood Those who had been fed on fats or proteins or who had been

TABLE 3—Results of Daily Tests of Tolerance of Rabbit 6 for Dextrose*

| Hours of Fasting and Toxemia | Temperature (F) Rectal | Blood Sugar, Mg per 100 Cc | | | |
|---------------------------------|------------------------------|----------------------------|----------------|------------|-------------|
| | | Fasting | After Dextrose | | |
| | | | 30 Minutes | 60 Minutes | 120 Minutes |
| 24 | 102.6 | 118 | 182 | 123 | 87 |
| 48 | 102.7 | 111 | 285 | 329 | 299 |
| 72 | 103.4 | 145 | 282 | 274 | 182 |
| 96 | 102.6 | 111 | 238 | 227 | 189 |
| 120 | 103.6 | 137 | 220 | 217 | 168 |
| 144 | 106 | 161 | 250 | 230 | † |

* The animal received 0.0075 cc of diphtheria toxin Two units of insulin were given subcutaneously each day fifteen minutes after the administration of dextrose

† Animal died during the one hour interval.

TABLE 4—Results of Daily Tests of Tolerance of Rabbit 7 for Dextrose (Control)

| Hours of Fasting | Temperature (F) Rectal | Blood Sugar, Mg per 100 Cc | | | |
|------------------|------------------------------|----------------------------|----------------|------------|-------------|
| | | Fasting | After Dextrose | | |
| | | | 30 Minutes | 60 Minutes | 120 Minutes |
| 24 | 101.7 | 101 | 180 | 150 | 89 |
| 48 | 102.1 | 102 | 169 | 179 | 132 |
| 72 | 103.7 | 140 | 179 | 145 | 114 |
| 96 | 103.8 | 118 | 148 | 114 | 63 |
| 120 | 103.8 | 129 | 204 | 171 | 92 |
| 144 | 103.4 | 56 | 89 | 64 | 58 |

* Diphtheria toxin was not given Two units of insulin were given subcutaneously each day fifteen minutes after the administration of dextrose

starved had had little if any foods (carbohydrates) that stimulated the production of insulin, and when dextrose was ingested the production of insulin was delayed, which resulted in a sluggish removal of the excess dextrose from the blood

It is difficult to explain the foregoing phenomena in any way except by the action of endogenous insulin If increased or decreased oxidation of the dextrose was the cause, one would have to account for the

7 Kageura, N J Biochem 1 333, 1922 Kageura, N J Biochem 1 389, 1922 Greenwald, I Gross, J, and Samet, J J Biol Chem 62 401, 1924 Southwood, A R M J Australia 10 460, 1923 Staub, H Ztschr f klin Med 93 89, 1922 Traugott K Klin Wchnschr 1 892, 1922 Du Vigneaud, Vincent, and Karr W G J Biol Chem 66 1 1925

effect of the antecedent diets on this process I cannot think of any reason why antecedent diets rich in sugars should cause a more rapid combustion of dextrose than diets consisting of fat or protein. The only other explanation apparent would be that there is a more rapid elimination of the excess sugar through the kidneys. This, however, cannot be held to be the explanation, because there was no postprandial sugar in the urine of the persons who had previously received the carbohydrate feedings.

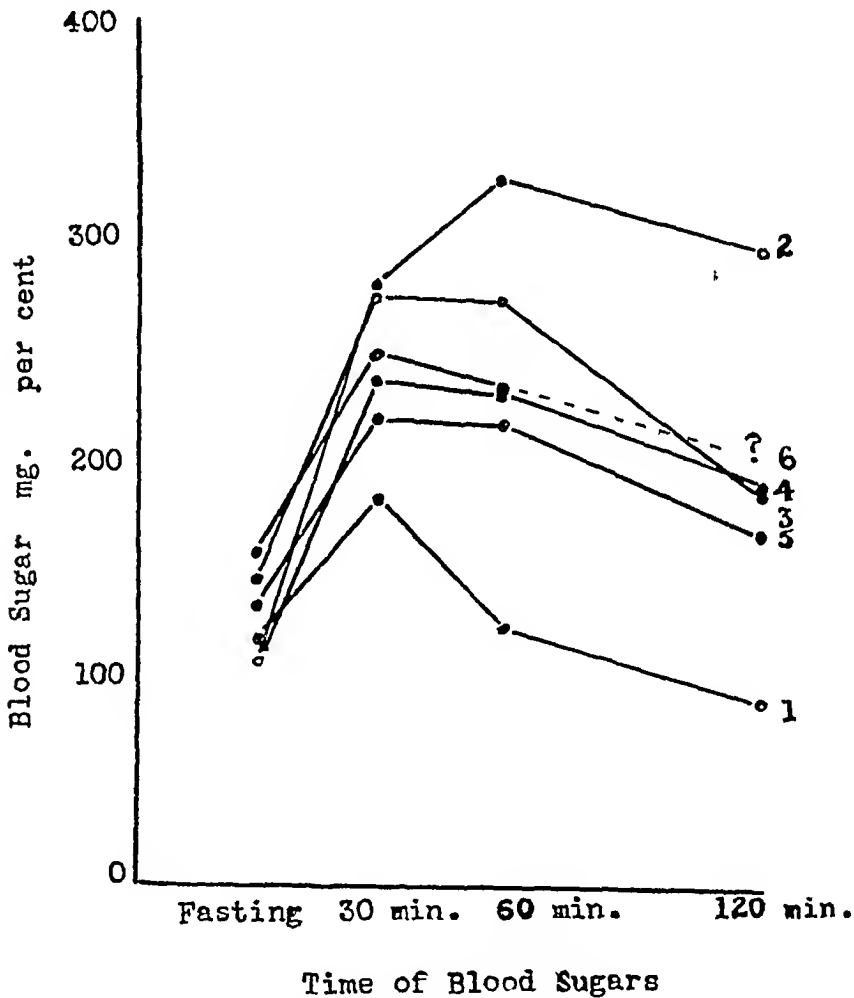


Chart 3—Daily curves showing tolerance of rabbit 6 for dextrose. The animal received 0.0075 cc of diphtheria toxin. Two units of insulin were given subcutaneously each day fifteen minutes after the administration of dextrose. The figures at the end of each curve represent the number of days of fasting and toxemia.

In another series of experiments referred to earlier in this paper, I¹ showed that there was a progressive decrease in tolerance for sugar by rabbits in the presence of an increasing toxemia. That toxemia causes a decrease in tolerance for sugar has long been known. Two theories have been suggested to explain this effect. Tisdall and his co-workers⁸

⁸ Tisdall, F. F., Drake, T. G. H., and Brown, Olan. Production of Lowered Carbohydrate Tolerance in Dogs, *Am J Dis Child* **32**: 854 (Dec.) 1926.

suggested that it is a result of an increase in the glycogenolytic function of the body or an impairment of the ability of the organism to store carbohydrates. Lawrence and Buckley⁹ have suggested that it is due to an increased glycogenolysis resulting from the stimulation of the “thyro-adrenal apparatus”. On the basis of what has been said in the preceding paragraphs, I am more inclined to explain the effect of toxemia by an impairment of the animals’ ability to store carbohydrates, which is but another way of saying that there is an impairment of glycogenesis. It is

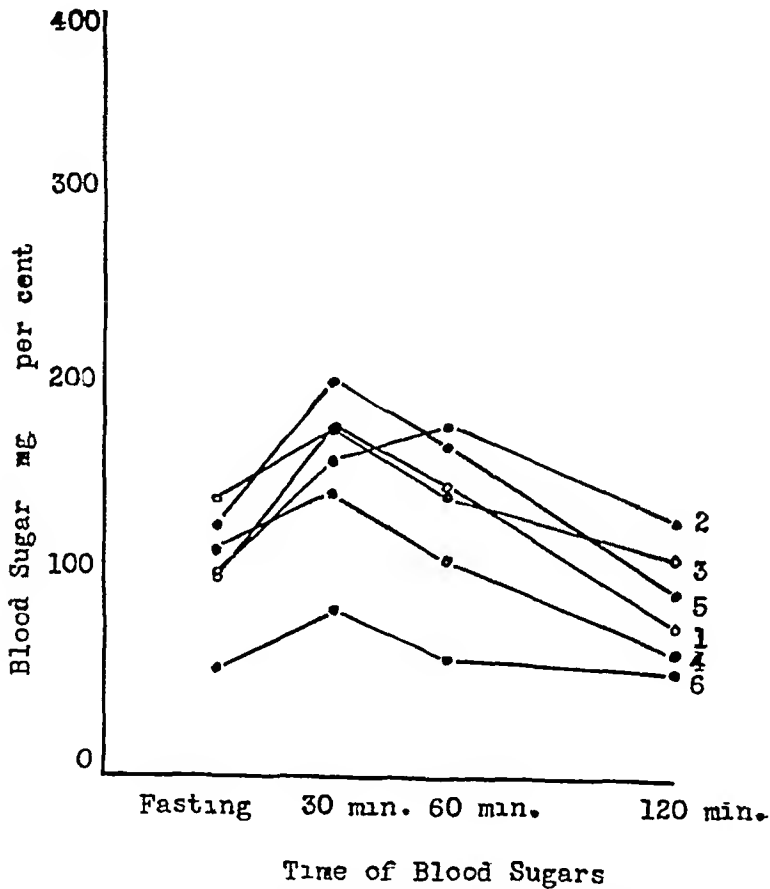


Chart 4—Daily curves showing tolerance of rabbit 7 for dextrose (control). Diphtheria toxin was not given. Two units of insulin were given subcutaneously each day fifteen minutes after the administration of dextrose. The figures at the end of each curve represent the number of days of fasting.

difficult to believe that glycogenolysis alone can account for the daily, progressively abnormal postprandial blood sugars observed in the toxic rabbits to which I have referred. If glycogenolysis was the cause, it would appear that dextrose itself might be stimulating that process, because the postprandial blood sugars rise to materially higher levels each day. I believe that the tendency for the blood sugars to be higher each day in fasting toxic animals is probably a result of glycogenolysis.

⁹ Lawrence, R. D., and Buckley, O. B. Brit J Exper Path 8 1, 1927

If it may be assumed, then, that the effect of toxemia is principally that of an impairment of an animal's ability to store carbohydrates, and if the storage of carbohydrates is brought about by endogenous insulin, it may be suggested that the toxemia has a direct depressing effect on the production of insulin. The experiments contained in this paper have demonstrated that the action of injected insulin is affected little if at all in toxic animals. The logical deduction, therefore, is that toxemia suppresses the endogenous production of insulin. From the experimental data at hand, this explanation seems to me to be more plausible than that of an increased glycogenolysis or a disturbed glycogenesis independent of endogenous insulin.

The hypothesis just outlined is consistent with certain clinical phenomena. For example, on this basis the onset of diabetes during or following acute infections might be explained. The occurrence of diabetes during pregnancy might be explained in like manner. The mechanism involved in such cases would be suppression of insulin production from an inherently weakened pancreas, due to toxemia. More and more attention is being paid to the rôle that heredity plays in the etiology of diabetes.¹⁰ The variation in the doses of insulin required to control diabetes in those suffering from infectious processes may be an expression of the toxic effects on the remaining functioning islands of Langerhans.

SUMMARY AND CONCLUSIONS

Daily tests of the tolerance for dextrose were made on rabbits in which toxemias had been produced with diphtheria toxin. Two units of insulin were injected daily fifteen minutes after the administration of dextrose. The toxemia appeared to have little, if any, effect on the injected insulin. On the basis of these and preceding experiments, it is suggested that the effect of toxemia is that of a suppression of endogenous production of insulin.

¹⁰ Von Noorden, C. Die Zuckerkrankheit und ihre Behandlung, ed. 8, Berlin, Julius Springer, 1927.

THE ICTERUS INDEX

SPECTROPHOTOMETRIC AND QUANTITATIVE STUDIES *

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The two quantitative clinical methods now available for estimating the degree of bilirubinemia are (1) the van den Bergh and (2) the icterus index. The latter, although simple, has the disadvantage in that the degree of jaundice is expressed in arbitrary units of icterus index, instead of in milligrams of bilirubin, one unit being the color equivalent of a 1/10,000 aqueous solution of potassium dichromate. It has been our aim in this work to inquire into the basic colorimetric relationships between potassium dichromate and various solutions of bilirubin and to assign, if possible, a definite value in milligrams of bilirubin to the dichromate dilutions. We have also investigated the effect of small amounts of hemolysis.

Murphy¹ and Davis² have adequately reviewed the history of the icterus index. It has long been assumed that bilirubin was the pigment responsible for jaundice, as spectrophotometric analyses of jaundiced serums correspond with the analyses of bilirubin made by Vierordt³ in 1876. Three years previously, he had published the results of analyses on serum showing an absorption band which was in the same region as bilirubin⁴. Sheard and his co-workers⁵ have also compared jaundiced serums with solutions of bilirubin in serum and have found them to be identical. We agree with these workers on the whole, although several of their statements will be discussed in the course of this paper.

* From the Department of Pathology, The University of Rochester School of Medicine and Dentistry.

1 Murphy, Wm P. An Easy Method of Estimating the Amount of Jaundice by Means of Blood Serum, Boston M & S J **194** 297 (Feb 18) 1926. Biliary System Function Tests, Arch Int Med **37** 797 (June) 1926.

2 Davis, D. The Determination of Icterus Index of Capillary Blood, Am J M Sc **172** 848 (Dec) 1926.

3 Vierordt, Karl. Die quantitative Spectralanalyse in ihrer Anwendung auf Physiologie, Physik, Chemie und Technologie, Tubingen, H Laupp, 1876.

4 Vierordt, Karl. Die Anwendung des Spectralapparates zur Photometrie des Absorptionsspektren und zur quantitative chemischen Analyse, Tubingen, H Laupp, 1873.

5 Sheard, C, Mann, F C, and Bollman, J L. Spectrophotometric Determinations of Purified Bilirubin, Am J Physiol **81** 774 (Aug) 1927. Magath, T B, and Sheard, C. Spectrophotometric Analysis of Blood Serum in Normal and Pathologic Conditions, Arch Int Med **39** 214 (Feb) 1927. Sheard, C, Baldes, E J, Mann, F C, and Bollman, J L. Spectrophotometric Determinations of Purified Bilirubin, Am J Physiol **76** 577 (May) 1926.

METHOD

For the purified bilirubin studied in this work we are indebted to Dr Hans Clarke in charge of the department of synthetic chemistry of the Eastman Kodak Company. A short description of the method of preparation is found in the paper of Sheard, Mann and Bollman.⁶

For the greater part of the studies on the quantitative analyses of the various solutions, we have used a Bausch and Lomb spectrophotometer Kennedy,⁷ from this laboratory, has recently described this particular instrument in detail. The photometer is of the Martens type with extinction points at 0 and 90 degrees and a match point close to 45 degrees. A slight constant deviation of the latter does not make any difference, as all of our solutions were examined first in one field and then in the other, and a sum of the two readings was taken. This instrument covers the visual range adequately. However, as our work has been with absorption bands in the violet end of the spectrum, where accurate visual readings are difficult, added accuracy has been obtained through the frequent employment of photographic records of the absorption bands. These records were obtained on a Hilger quartz spectrograph, the property of the Research Laboratory of the Eastman Kodak Company through the courtesy of Dr C E K Mees, director of the laboratory, and the efforts of Messrs E E Richardson and Floyd Hertle, who have done the analytic work.

POTASSIUM DICHROMATE

Our stock solution of potassium dichromate was prepared by dissolving 10 Gm of chemically pure crystals in a liter of distilled water. To this solution 2 drops of concentrated sulphuric acid were added, as recommended by Meulengracht.⁸ We believe this to be of importance, as a slight amount of alkali changes the dichromate to chromate with a corresponding change in color, the latter being more yellow and thus leading to considerable error. This change is particularly apt to go unnoticed in the more dilute solutions. Chart 1 expresses graphically the absorption of 1 Gm of potassium dichromate per liter, with 2 drops of sulphuric acid per liter and also the absorption of the same dilution of dichromate with 1 drop of concentrated sodium hydroxide to 100 cc of solution. This dilution of dichromate, which has an icterus index of 10, has a rather low optical density in the visual region, nevertheless, the curve of the absorption band is extremely steep in the region in which we are interested, from 460 to 430 millimicrons, and from the chart it will be seen that the maximum absorption is in the ultraviolet end of the spectrum, where this dilution gives an optical density greater than 2.3, the limit at which the Hilger spectrograph was set.

6 Sheard (footnote 5, first reference)

7 Kennedy, R P. A Spectrophotometric Study of Blood Solutions, *Am J Physiol* **79** 346 (Jan) 1927

8 Meulengracht, E. Ein Bilirubinkolorimeter behufs klinischer Bestimmung der Bilirubinmenge im Blute, *Deutsches Arch f Klin Med* **137** 38 (Aug 12) 1921

It will be seen that the addition of alkali has definitely changed the color, since the absorption band is moved toward the ultraviolet. As we should expect, this corresponds with the absorption band of potassium chromate. Once prepared, the dichromate keeps well, for there was not any perceptible change when it was kept in the dark for two months or when it was exposed to the light for a similar length of time.

BILIRUBIN

The chemical composition of bilirubin is still uncertain, but it probably has the formula $C_{32}H_{36}N_4O_6$, containing two carboxyl groups which make it a weak acid⁹. The sodium salt is much more soluble than the acid itself.

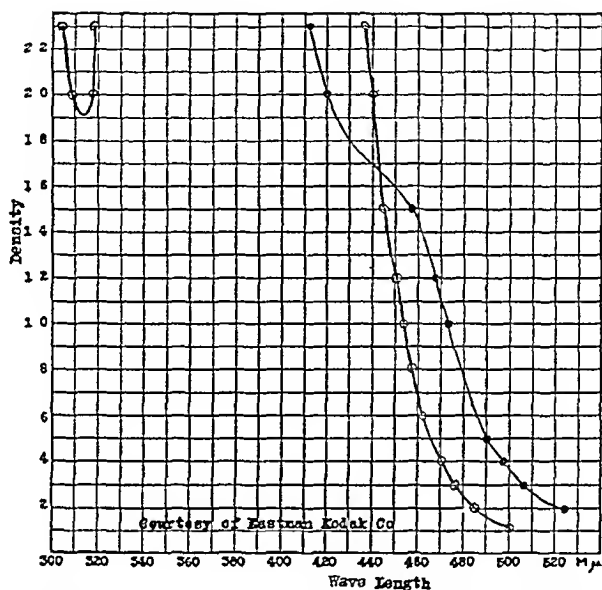


Chart 1—Graph showing the absorption of potassium dichromate. The line with the dark circles indicates the absorption of 1 Gm per liter of potassium dichromate with 2 drops of sulphuric acid per liter, the line with the light circles indicates the absorption of 1 Gm per liter of potassium dichromate with 1 drop of sodium hydroxide to 100 cc of solution.

The purified bilirubin with which we worked was insoluble without the addition of alkali in the serum of both man and dog. As we were not certain that bilirubin occurs in nature as the salt or that the salt and the acid are photometrically identical, a number of different solvents were tried. These included chloroform, absolute ethyl alcohol, acetone, a mixture of alcohol and acetone 3:1, the same mixture made alkaline, various aqueous buffer solutions and dog serum. The observations with these solvents are summarized.

⁹ Orndorff, W. R., and Teeple, J. E. On Bilirubin, the Red Coloring Matter of the Bile, *Am. Chem. J.* 33: 215 (March) 1905.

Bilirubin in Chloroform—The quality of chloroform used was that generally described as "for anesthesia" and put up in brown glass bottles. No difference was noted between Squibb's and Mallinckrodt's, the two preparations used. Fifty milligrams of bilirubin was completely dissolved in 200 cc of chloroform at the end of three days in the incubator at a temperature of 37.5 C. If the solution was kept in the icebox, the time required for the bilirubin to dissolve was somewhat longer. This stock solution was kept in dark brown, glass-stoppered bottles, and sealed with paraffin. As the stock solution was too dense for spectrophotometric examination, various dilutions were made containing from 8 to 40 mg per liter, the optimum for analysis being 20 mg.

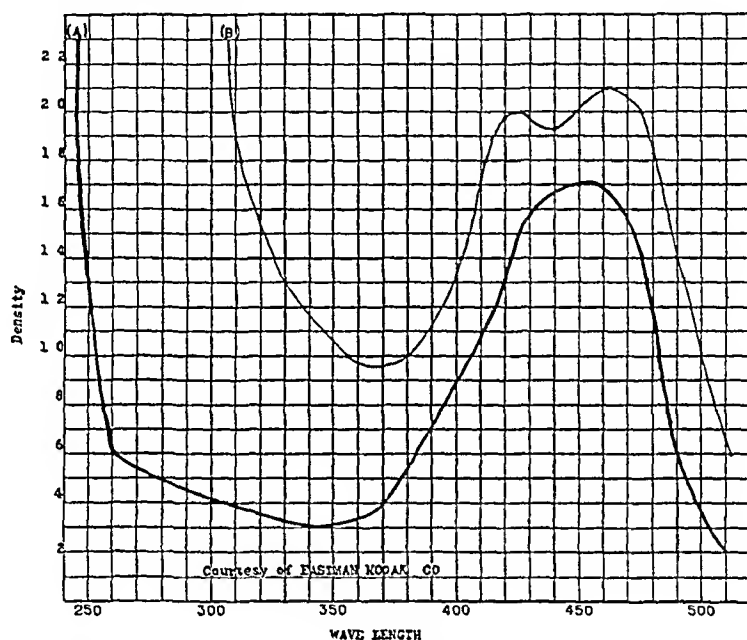


Chart 2—Curves showing *A* the absorption of 20 mg per liter of bilirubin in chloroform and *B* the absorption of 16 mg per liter of bilirubin in dog serum. The stock solution of bilirubin in serum contained 25 mg of bilirubin in 50 cc of serum, 25 cc of hundredth-normal sodium hydroxide and 25 cc of hundredth-normal hydrochloric acid. The dilution contained 16 mg per liter and 96.8 per cent serum density of 0.55 at 450 millimicrons.

A chloroform solution of bilirubin contains two absorption bands, one in the visible spectrum and one in the ultraviolet. There is almost complete transmission of red, orange and yellow light and some transmission of green light. Beginning at a wave length around 520 millimicrons in the region of the green, however, it rapidly absorbs increasing amounts of green and blue rays, the maximum absorption being around 450 millimicrons. The absorption decreases throughout the violet and into the ultraviolet, the maximum transmission occurring in the region of 350 millimicrons, when at first gradually and then more sharply the absorption rises to a maximum in the region of 250 millimicrons. The curve is shown in chart 2. This curve is not in accord with Vierordt's

observations on a visual instrument, as he obtained increasing densities up to 430 millimicrons³ and even at 410 millimicrons¹⁰ where his curve ends. Even at 450 millimicrons it is difficult to make comparisons. This difficulty increases markedly the nearer the ultraviolet is approached, until at 420 millimicrons readings are, in our experience, impossible, due to the physiologic limits of the eye. The relative visibility of the human eye has been accurately determined for the different wave lengths. At 450 millimicrons it is approximately 3.8 per cent of that at the maximum, which is at 556 millimicrons, at 420 millimicrons it is only 0.4 per cent of the maximum¹¹. We have never tried to read below 440 millimicrons, and for 440, 450 and 460 millimicrons, we have taken the average of a number of readings. It has not been uncommon to find a maximum deviation of optical density at 450 millimicrons of from 5 to 6 per cent from the mean. It is obvious that the photographic records for the spectral region from 400 to 440 millimicrons constitute the most accurate method available. For one other reason we believe our visual readings are more accurate than those of Vierordt. With our instrument we have been able to work with an ocular shutter width such that the field we are examining at 450 millimicrons is only from 0.8 to 1 millimicron in width. Judging by certain of Vierordt's charts, we believe that from this region to 430 millimicrons he was working with a field from 5.5 to 34 millimicrons in width. Obviously, when examining the edge of an absorption band where the slope is steep, the narrower the field the more accurate the determination.

For every true solution there is a quantitative relationship between the absorption of light and the concentration of the solution. The factor which expresses this quantitative relationship is usually designated as the absorption ratio "A" which is a constant for a particular substance in the same solvent at a given wave length. The relationship may be expressed by the equation $C = A \times \frac{D}{H}$ in which C is the molecular concentration, A, the absorption ratio, D, the optical density (logarithm of opacity, opacity being the reciprocal of the transmission) and H, the thickness. In all of our readings we have used a cell of uniform thickness, 1 cm. Therefore, $H = 1$ and $C = A \times D$ and $A = \frac{C}{D}$.

Using this formula and expressing "C" in milligrams per liter, we have determined the ratio of absorption for bilirubin in chloroform at 450 millimicrons, and have found it to be 11.4, this being an average of the readings of four different observers in this laboratory during the course of sixteen months. All observations were made on freshly pre-

10 Kruss, Gerhard and Hugo. *Kolorimetrie und quantitative Spektralanalyse*, Leipzig, Leopold Voss, 1909.

11 Illuminating Engineering Nomenclature and Photometric Standard Transaction, Eng. Soc. 20:632 (July) 1925.

paired chloroform solutions of purified bilirubin with concentrations varying from 8 to 20 mg per liter. There is a maximum deviation from the mean of 9.5 per cent and an average deviation of 5.5 per cent. Considering the part of the spectrum in which we are working, we do not regard this as excessive.

In table 1 our determinations are compared with those obtained from two other sources. The first are the ratios computed from the readings furnished us by the Eastman Kodak Company obtained on their quartz spectiograph. Two observations each gave a ratio of 11.77. The second set of figures are by Vierordt quoted by Kruss¹⁰. It is

TABLE 1—*Absorption Ratios of Bilirubin in Chloroform*

| Observer | Date | Mg per Liter | Wave Length | D | A = C/D |
|-----------------------------------|---------|--------------|---------------|-------|---------------|
| R P K | 3/10/26 | 10 | 449.5 - 450.5 | 0.882 | 11.35 |
| W W | 4/7/27 | 20 | 449.5 - 450.5 | 1.73 | 11.56 |
| E E | 6/28/27 | 20 | 449.5 - 450.5 | 1.935 | 10.35 |
| F E | 6/28/27 | 10 | 449.5 - 450.5 | 0.829 | 12.05 |
| L E | 6/28/27 | 15 | 449.5 - 450.5 | 1.192 | 12.60 |
| E E | 6/28/27 | 8 | 449.5 - 450.5 | 0.655 | 12.22 |
| C O | 7/7/27 | 20 | 449.5 - 450.5 | 1.851 | 10.77 |
| O O | 7/11/27 | 20 | 449.5 - 450.5 | 1.816 | 11.00 |
| F F | 7/12/27 | 20 | 449.5 - 450.5 | 1.918 | 10.42 |
| E L | 7/13/27 | 20 | 449.5 - 450.5 | 1.710 | 11.67 |
| Mean value for A | | | | | 11.40 |
| Maximum deviation from mean for A | | | | | 9.5 per cent |
| Average deviation from mean for A | | | | | 5.5 per cent |
| E K Co | 7/28/27 | 20 | Approx. 450 | 1.700 | 11.77 |
| E K Co | 7/29/27 | 20 | Approx. 450 | 1.700 | 11.77 |
| Mean value for A | | | | | 11.77 |
| Vierordt | 1876 | 5 | 437 - 450 | 0.475 | 10.53 |
| Vierordt | 1876 | 5 | 450 - 462 | 0.469 | 10.67 |
| Vierordt | 1876 | 12.5 | 450 - 462 | | 12.23 |
| Mean value for A | | | | | 11.14 |
| Maximum deviation from mean for A | | | | | 9.79 per cent |
| Average deviation from mean for A | | | | | 6.48 per cent |

D indicates the optical density (negative logarithm of transmission), C, the concentration in milligrams per liter, E, the extinction coefficient (equal to D when thickness of cell containing solution is 1 cm.) and A, the ratio of absorption (equal to C/D).

rather difficult to compare these figures accurately as they have to be correlated with our readings of the wave length. The field examined was wide, and the ratio differed markedly for different concentrations. As we have averaged them, however, the ratio of absorption is 11.14 with a maximum deviation of 9.79 per cent.

Instability of Chloroform Solution of Bilirubin—We have had a concentrated solution of bilirubin in chloroform (50 mg per hundred cubic centimeters) in an icebox for seventeen months. It was kept in a brown, glass-stoppered bottle. During that time it had faded approximately 20 per cent as judged by single dilutions prepared at each end of the period. We have kept dilute solutions 20 mg per liter in the dark for six weeks, and have found at the end of two weeks that the readings were identical within the limits of error, while at the end of four and

six weeks there was definite fading of from 7 to 10 per cent Richardson¹² said that he had detected obvious fading in such a solution in three days when kept in the dark. When exposed to the light, even subdued light, the color fades rapidly. It has been our experience that when a tightly corked test tube containing a solution of 20 mg per liter is left in the light of a northern window on a bright day, where there are no direct sun rays, the color will have faded so much in six hours that it is impossible to make a spectrophotometric analysis. The same solution, which showed a fading of only 7 per cent when kept in the dark for six weeks, showed a fading of 12 per cent of the remainder when left in the beam of the spectrophotometer for four hours, the source of light being a 250 watt bulb. It is obvious that analyses on freshly prepared solutions of bilirubin should be made quickly, and that at all other times the bilirubin should be kept in the dark.

Acetone—Five milligrams of bilirubin were partially dissolved in 100 cc of acetone at the end of one week at room temperature. There was no more in solution at the end of six weeks. The curve resembled the chloroform curve. The maximum optical density occurred at 450 millimicrons and, with a 1 cm layer, averaged 0.67.

Absolute Alcohol—Five milligrams of bilirubin remained practically undissolved in 100 cc of absolute ethyl alcohol at the end of six weeks. There was insufficient color in the solute to permit an analysis. It is to be remembered that in the preparation of purified bilirubin Orndorff and Teeple⁹ found that it was insoluble in absolute alcohol.

Absolute Alcohol, Alkaline—To the foregoing solution we added 1 cc of tenth-normal alcoholic sodium hydroxide (the hydroxide being dissolved in 95 per cent alcohol). The bilirubin immediately went into solution. It was diluted to 20 mg per liter, and a spectrophotometric analysis was made. The point of maximum absorption was still at 450 millimicrons, but the curve did not seem so steep as that when chloroform was used. The optical density, too, was only 1.17, much less than any equivalent concentration in chloroform.

Alcohol (3 parts of 95 per cent) — Acetone (1 part) Mixture—Twenty-five milligrams of bilirubin remained practically undissolved in 100 cc of alcohol-acetone mixture for three days. Owing to the turbidity of the solution, curves were not made.

Alcohol-Acetone, Alkaline—To the foregoing mixture we added 1 cc of tenth-normal alcoholic sodium hydroxide. The bilirubin immediately dissolved. This alkaline mixture was then diluted with the stock alcohol-acetone mixture to a concentration of 10 mg per liter, and a

12 Richardson, E. E. Research Laboratory Eastman Kodak Company, personal communication to the authors.

curve was made. Like the alkaline alcoholic curve the optical density was not so great as when an equivalent chloroform dilution was used, and the curve was not so steep.

Aqueous Solutions.—Five milligrams of bilirubin were practically undissolved in distilled water at the end of a week. It immediately went into solution on the addition of a few drops of concentrated sodium hydroxide. Various buffer solutions were made, and several rough colorimetric calculations of f_H were made according to the method of Clark and Lubs¹³. It was found that bilirubin would quickly dissolve in a weak solution of sodium carbonate, with a f_H unknown but greater than 9.5. It remained undissolved in a solution of disodium phosphate with a f_H around 9.6.

These solutions were much more unstable colorimetrically than the solutions in chloroform. When test tubes containing these dilutions were brought into daylight in test tube racks so constructed that the lower portion of the tube was partially protected from the light, it was found that the portion of the solution exposed to the light had become practically colorless at the end of two hours while the solution in the lower portion of the tubes still contained much of its color.

DYES

In view of the fact that the curves showing the absorption of bilirubin and potassium dichromate are obviously different, an attempt was made to find a yellow dye which would more nearly resemble bilirubin. Aqueous solutions of quinoline yellow, fast yellow, flavazine and chrysoidine Y were prepared. The absorption spectra of all of these with the exception of chrysoidine Y differed markedly from that of bilirubin. On theoretical grounds chrysoidine should be fairly satisfactory, as its maximum absorption occurs in the region of 450 millimicrons the same as bilirubin and the curve is fairly sharp but unfortunately the aqueous solution does not match jaundiced serum nearly so well as potassium dichromate, which, despite its theoretical disadvantages works surprisingly well and will probably continue as a standard until a better one has been developed.

BILIRUBIN DISSOLVED IN DOG SERUM

As this problem is particularly concerned with bilirubinemia, it was thought advisable to measure the color or to determine the absorption curve of definite known amounts of bilirubin in known amounts of serum. A serum which does not contain any pigments would be ideal for this purpose. As dog serum contains comparatively little and is easily available, it was used.

¹³ Clark, W. M.: *The Determination of Hydrogen Ions*. Baltimore, Williams & Williams Company, 1922.

Healthy stock dogs were used, and from 100 to 300 cc of blood was drawn by suction directly into 100 cc centrifugal tubes under liquid petrolatum. The blood was drawn from twelve to twenty-four hours after a meal. These tubes were left at room temperature for two hours, and the blood was then centrifugalized. Any tubes showing hemolysis or undue turbidity were discarded. The remaining serum was pooled, and a complete spectrophotometric curve was made covering not only the region of absorption of bilirubin but also that of hemoglobin.

As recorded by Sheard, Mann and Bollman,⁶ this bilirubin is insoluble in serum without the addition of alkali. We followed a slightly different procedure than they. We dissolved 25 mg of purified bilirubin in 25 cc of hundredth-normal sodium hydroxide. This amount was then quickly dissolved in 50 cc of serum, and any tendency toward alkalinity was neutralized by the addition of 25 cc of hundredth-normal hydrochloric acid. Owing to the presence of the serum, these stock solutions did not keep indefinitely, but rather became turbid after remaining in the icebox. Dilutions were immediately made from these stock solutions, however, both serum and salt solution being used.

The spectrophotometric curve of bilirubin dissolved in serum differs from that of bilirubin dissolved in chloroform. Possibly this is because in chloroform the bilirubin is present as such, while in the serum it may be present as a salt. At any rate, bilirubin in serum has an absorption band in the visible spectrum with a point of maximum absorption between 460 and 470 millimicrons with a lesser peak between 420 and 430 millimicrons and a depression in the hump in the region of 440 millimicrons. In the ultraviolet end of the spectrum, there is a marked difference in the two curves. The solution of chloroform has its band of maximum absorption in the region of 250 millimicrons, while the solution of serum has its maximum absorption in the region of 310 millimicrons. The point of minimum optical density in the ultraviolet in the solution of chloroform occurs around 340 millimicrons and is rather low. In the dilution of serum it occurs at 370 millimicrons and is relatively high. Chart 2 illustrates the differences in these curves both in the ultraviolet and in the visual up to 510 millimicrons.

We note that this curve does not agree with the observations of Sheard, Mann and Bollman⁵ who give an increasing density for bilirubin in alkaline serum up to 430 millimicrons. These same observers with their co-workers find that bile and jaundiced serum have an increasing density up to 430 millimicrons and even to 420 millimicrons, at which point their curves end. Occasionally, we have found a dilution of bile from the gallbladder which apparently has a greater absorption at 440 than at 450 millimicrons. We have uniformly found that normal serum, jaundiced serum and jaundiced ascitic fluid have their maximum absorption at 450 millimicrons.

We have also determined the absorption ratio for bilirubin dissolved in serum at 450 millimicrons. In all figuring it was necessary to take account of the effect of the turbidity and the bilirubin present in the normal serum used as the solvent and diluent. Two separate methods of doing this were employed. The simplest method was to fill one cup of the spectrophotometer with the solution to be examined and to fill the other cup with the diluting serum. As all of the dilutions we studied in the spectrophotometer contained from 96 to 99.2 per cent of this serum, the error due to varying amounts of serums was negligible. The other method we used was to fill one cup of the spectrophotometer with the solution to be examined and the other cup with water. This necessitated making an examination of the serum and subtracting from every reading for the unknown solution a calculated correction for the presence of the serum. The results from these two methods were comparable. Dilutions ranging from 2 to 20 mg. per liter were prepared from three separate stock solutions, and the absorption ratio of $A = 10.88$ was determined for a wave length of 450 millimicrons. On eighteen readings there was an average deviation from the mean of 3.25 per cent and a maximum deviation of 8.5 per cent. We would again stress the importance of making readings only on freshly prepared solutions, since these solutions rapidly become turbid and since turbidity markedly increases the density.

An attempt was now made to assign definite values in milligrams of bilirubin to the various dilutions of dichromate. These dilutions were made as outlined by Murphy¹⁴ with indexes ranging from 1 to 100. Wassermann tubes of a uniform internal bore of 12.5 mm. were filled with these solutions, corked, labeled and sealed with paraffin. Thus sealed they keep indefinitely. For reading our indexes we have constructed a small wooden box 17 by 8.5 by 3.5 cm. Six holes 16 mm. in diameter, were bored in one of the narrower sides. The Wassermann tubes fit snugly into these holes and sit in depressions on the opposite side of the box, thus firmly fixing the tube. Six parallel longitudinal slots 7.5 mm. in width were cut through the wide side of the box, the center of the slot being directly over the midline of the tube. Small wooden partitions separate the spaces for the tubes into compartments. The whole box is painted black. There is no ground glass or other backing to the box, all readings being made against a northern sky by daylight.

Various dilutions of bilirubin in serum were then made containing from 1 to 100 mg. of bilirubin per liter. The approximate icterus index of each of these dilutions was then determined. A more accurate comparison was then made using a Duboscq colorimeter as advocated by

14 Murphy (footnote 1, second reference)

Bernhardt and Maue¹⁵ In every case the serum was matched as an unknown against an approximately equivalent dichromate solution. The dichromate was set at 10, and the readings for the serum were determined. From this reading the equivalent value of dichromate in icterus index (hundreds of milligrams of dichromate per liter) was determined. In each case, however, it was necessary to make a correction for the amount of bilirubin present in the normal serum before the bilirubin was dissolved. This correction was merely a subtraction of the icterus index of the normal serum previously determined. Thus, potassium dichromate (icterus index 5 containing 500 mg per liter) set at 10 is matched by synthetic serum containing 6 mg of bilirubin per liter set at 8.1

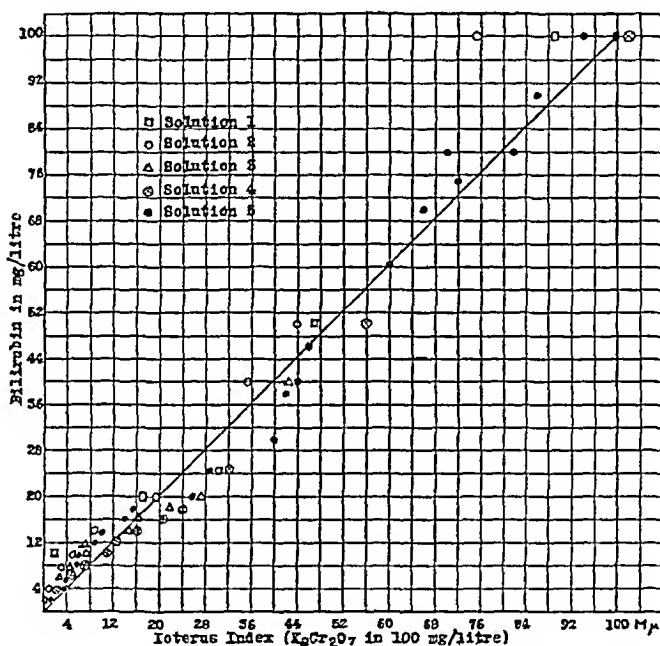


Chart 3—Graph showing concentration of bilirubin in milligrams per liter plotted as ordinates against dilutions of potassium dichromate plotted as abscissas

Serum containing 6 mg bilirubin $= \frac{5 \times 10}{8.1} = 6.17$ icterus index. The normal serum, however, which was used as the solvent and diluent was known to be equivalent to an icterus index of 2.1. Therefore, 6 mg bilirubin per liter $= 6.17 - 2.1 = 4.07$ icterus index.

Chart 3 is a graph in which the concentrations of bilirubin expressed in milligrams per liter are plotted as ordinates against dilutions of potassium dichromate plotted as abscissas. Five separate solutions of bilirubin in serum were thus matched and fifty-seven points recorded.

¹⁵ Bernhardt and Maue, cited by Stetten, DeWitt. The Surgical Value of the Estimation of the Bile Pigmentation (Icterus Index) of the Blood Serum, *Ann Surg* **76** 191 (Aug) 1922.

It will be noted that a straight line drawn through the maximum number of points is almost an exact diagonal of the graph. In other words, an icterus index of 100 is equivalent to 100 mg of bilirubin per liter, an icterus index of from 50 to 50 mg of bilirubin per liter and an icterus index of 16 to 16 mg per liter. In the weaker dilutions the percentage of error is increasingly higher, and with an icterus index of 6 or below, the error may be marked. It will be seen, however, that the error is greatest in the range of normal serum, and that the comparison becomes increasingly accurate the more jaundiced the serum.

We know that the normal serum has an icterus index of from 3 to 8, usually from 4 to 6. Estimating from our graph, we would assign to these indexes values of from 4 to 10 mg of bilirubin per liter. This is in accord with what certain other workers have assumed¹⁶. Why this relationship should obtain between two substances with such different absorption spectra we cannot explain. We do know, however, that this same relationship does not obtain between potassium dichromate and the chloroform solutions of bilirubin. Although dichromate has a greater absorptive power for light than the bilirubin solution with which it matches, it is probable that the absorption is, for the greater part, toward the extreme violet and the ultraviolet end of the spectrum beyond the region of perception by the eye, and that the transmitted light integrates to give the same visual effect.

Turbidity—Two of the chief obstacles to accurate quantitative determinations of pigment in serum are turbidity and hemolysis. Any method which would eliminate either of these would make for much greater accuracy. Ernst and Forster¹⁷ have apparently used both alcohol and acetone separately to precipitate the proteins and to clear the serum. Magath, Sheard, Mann, Bollman and Baldes⁵ have used a mixture of alcohol (4 parts) and acetone (1 part) later changed to 3:1 for the same purpose.

We have tried alcohol and acetone separately, alcohol-acetone mixtures and an alcohol-acetone mixture made alkaline. We have used one or all of these on jaundiced serum, both human and dog, on diluted bile (obtained at autopsy), on bilirubin dissolved in serum and on bilirubin dissolved in chloroform. All of these precipitants reduce the turbidity of serum, but in every case they precipitate a certain amount of pigment. Chart 4 presents graphically our experiences with four of these solutions, namely, jaundiced serum of man and dog, diluted bile and bilirubin dissolved in chloroform.

¹⁶ Forster, J. Ueber Die normalen Werte Des Bilirubingehaltes im Blutserum, *Klin Wchnschr* 4 1689 (Aug 27) 1925.

¹⁷ Ernst, Z., and Forster, J. Ueber die Bestimmung des Blutbilirubins, *Klin Wchnschr* 3 2386 (Dec 23) 1924.

In every case the substance examined was diluted with physiologic sodium chloride to a concentration which could be easily read. Identical dilutions were then made with the various mixtures as indicated. All tubes were allowed to stand for two hours and the solution was then centrifugalized, the supernatant fluid was analyzed and the readings were recorded. In most cases the remaining solution was allowed to stand for twenty-two hours more, it was again centrifugalized and analyzed. In every case there was more fading at the end of twenty-four

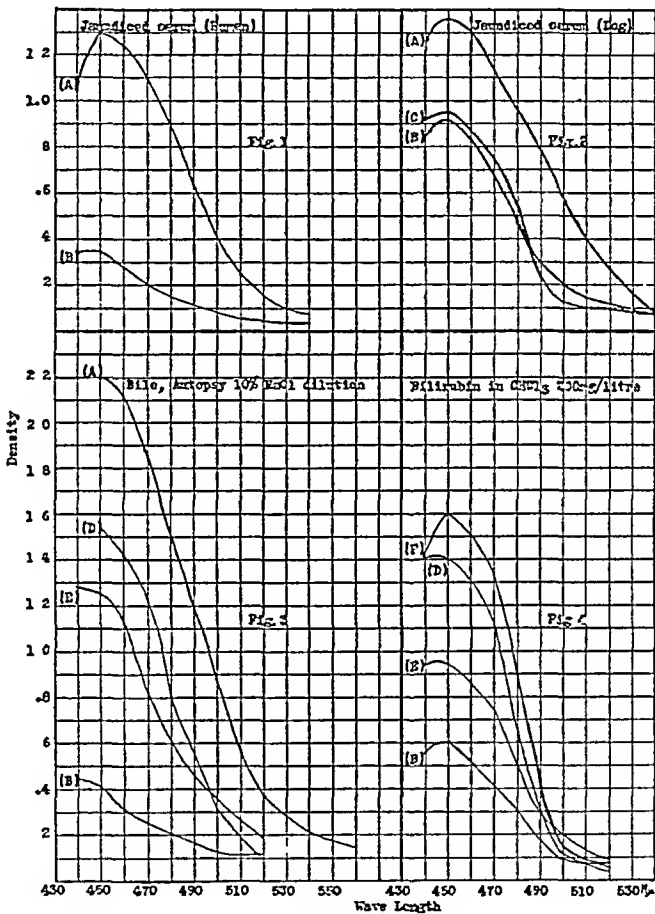


Chart 4—Curves showing the effect of precipitants on various solutions of bilirubin. A indicates the curve when saline was used, B, alcohol-acetone, C, alkaline alcohol-acetone, D, acetone, E, absolute alcohol and F, chloroform. In figures 1 and 2 the dilution was 1/4, in figure 3, 2/1 and in figure 4, 1/9.

hours than at the end of two hours. That this precipitation is a matter of importance is illustrated in chart 4 (fig. 1), which shows a loss of color in jaundiced serum of over 70 per cent due to the precipitation with the alcohol-acetone mixture. Diluted bile showed a loss of over 80 per cent of the total pigment due to the alcohol-acetone mixture (chart 4, fig. 3). In no case have we found more color lost than that already recorded, in many cases considerably less. In certain instances alcohol

or acetone alone have apparently made little difference (chart 4, fig 4) In chart 4 (fig 2) we have also recorded the effect of making the alcohol-acetone mixture distinctly alkaline (1 cc of tenth-normal alcoholic sodium hydroxide to 100 cc of alcohol-acetone mixture) It has apparently not altered the fact that the mixture precipitates a large amount of pigment, in this case over 30 per cent In view of the fact that we have demonstrated the relative insolubility of bilirubin in these various solvents without the addition of alkali, we do not think it at all surprising that this precipitation should occur In this connection it is interesting to speculate on the accuracy of the van den Bergh reaction, which requires the addition of two volumes of 96 per cent alcohol to one volume of serum to precipitate the proteins before any attempt is made to estimate the "units of bilirubin" ¹⁸ Bernheim has also hinted at this inaccuracy ¹⁹ Further comment is made by Perkin ²⁰

In their latest communication ⁵ Sheard, Mann and Bollman say that they have found it necessary to add alkali to the alcohol-acetone mixture when working with the purified bilirubin They also say that when working with the serums of normal and jaundiced dogs they have added only the alcohol-acetone mixture They apparently content themselves with the statement that "Tests have demonstrated that the solutions prepared in this manner are slightly alkaline" They do not state whether they have compared the bilirubin content of these dilutions with control dilutions Using these precipitants, we too have found transmissions of 90 per cent or better (density 0.05 and less) in the region between 500 and 700 millimicrons, but by this method we have precipitated from 30 to 80 per cent of the pigment, This error is many times greater than that due to the turbidity present in carefully collected serum

Effect of Hemolysis—We cannot agree with the statement of Brown ²¹ that slight hemolysis does not vitiate the icterus index test We have taken jaundiced serum and made various saline dilutions giving an icterus index range of from 1 to 50 Five cubic centimeters of these dilutions was pipetted into our icterus index tubes These were read and recorded The blood of a normal dog was taken in liquid oxalate such that it contained 9 Gm of hemoglobin per hundred cubic centimeters A 10 per cent hemolyzed solution of this was made in 0.4 per cent ammonia Then a dropper freeing 25 drops per cubic centimeter was

18 Van den Bergh, A. A., and Snapper, J. Die Farbstoffe des Blutserums, *Deutsches Arch f klin Med* **110** 540 (May) 1913

19 Bernheim, A. R. The Significance of Variations of Bilirubinemia, *Arch Path* **1** 747 (May) 1926

20 Perkin, F. S. Blood Bilirubin, Estimation and Clinical Significance, *Arch Int Med* **40** 195 (Aug) 1927

21 Brown, A. L. Rapid Clinical Method for Determination of Icterus Index, *Arch Path* **3** 409 (March) 1927

used, a drop of blood being placed in each tube and the icterus index read. Additional drops were added one at a time to each tube until the hemolysis could be easily seen. The latter point, being a matter of individual decision, is subject to wide variation, and although at the points we have decided on there are relatively large amounts of hemoglobin, we doubt if the ordinary observer would detect amounts much below these points. Frequently before we could detect any hemolysis grossly we could determine that the solution was definitely off color, but below this point the addition of hemoglobin simply raised the icterus index reading of different dilutions. This is graphically expressed in table 2. It is interesting to note that although the hemolysis is first noticed in the lower ranges, from icterus index 1 to icterus index 5, it affects the readings in this region little if at all. Above icterus index 7,

TABLE 2—*Icterus Indexes of Various Dilutions of Jaundiced Serum With and Without the Addition of Hemolyzed blood (1 Drop Blood = 0.007 Per Cent)*

| Icterus Index of Serum | Serum Plus 0.007% Hemoglobin | Serum Plus 0.014% Hemoglobin | Serum Plus 0.021% Hemoglobin | Serum Plus 0.028% Hemoglobin | Serum Plus 0.035% Hemoglobin | Hemolysis Evident, per Cent of Hemoglobin |
|------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|---|
| 1-2 | 2 | 2 | * | | | 0.023 |
| 2-3 | 2-3 | 2-3 | 2-3 | * | | 0.035 |
| 3-4 | 3-4 | 3-4 | 3-4 | * | * | 0.042 |
| 4-5 | 4-5 | 4-5 | 4-5 | * | * | 0.049 |
| 7-8 | 8-10 | 10-12 | 10-12 | * | * | 0.033 |
| 8-10 | 12-15 | 12-15 | 12-15 | 15-20 | * | 0.077 |
| 12-15 | 15-20 | 20-25 | 25 | 35 | * | 0.084 |
| 15 | 15-20 | 25-35 | 25-35 | 35-50 | * | 0.084 |
| 15-20 | 20-25 | 35 | 35-50 | 50-75 | 75-100 | 0.084 |
| 20-25 | 25-35 | 35-50 | 50 | 75-100 | 100 | 0.084 |
| 25-35 | 35-50 | 50-75 | 75 | 100 | 100 | 0.077 |
| 35-50 | 35-50 | 50-75 | 75-100 | 100 | 100 | 0.070 |

* Solution off color.

Bold faced figures denote the nearest index.

however, the readings are increased even with one drop of the 10 per cent solution of hemolyzed blood which is a concentration of hemoglobin of 0.007 per cent (1:14,000).

Kennedy²² has recently discussed the value of light filters in colorimetry. As two of the absorption bands of hemoglobin occur in an entirely different part of the spectrum, 540 and 575 millimicrons, it was thought that if the solutions could be compared through a light filter which would cut out rays of a greater wave length than 500 millimicrons and yet have a high transmission in the region of 450 millimicrons, at least a part of the effect due to the hemoglobin could be ruled out. The Wratten light filter no. 47 made by the Eastman Kodak Company seemed to fulfil these requirements. It is a blue filter which effectively cuts out

22 Kennedy, R. P. The Use of Light Filters in Colorimetry with a Method for the Estimation of Hemoglobin, *Am J Physiol* **78**:56 (Sept) 1926.

the bands of hemoglobin at 540 and 575 millimicrons. There is another band of hemoglobin the same as bilirubin in the region 450 millimicrons. Obviously, no light filter can be expected to differentiate between this band and the band of bilirubin. Our only objection to filter no. 47 is that even at 450 millimicrons there is an optical density of approximately 0.3. Dr. Mees kindly provided us with a special blue filter 846-2 which is as effective in removing the lines of hemoglobin, and which at the same time has a density of approximately 0.1 in the region of 450 millimicrons. Chart 5 illustrates how light filter 846-2 excludes light rays in the region of two of the bands of hemoglobin, while giving a high transmission in the region of maximum absorption of bilirubin. In reading the solutions it apparently made little difference whether the filter was held in front of the eye with the solutions at arms length or whether the filter was

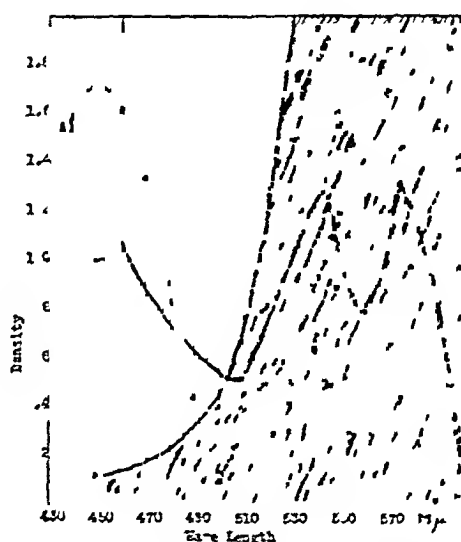


Chart 5—Graph showing how light filter excludes light rays in the region of two bands of hemoglobin but yet has high transmission in region in which bilirubin has great absorption. A indicates bilirubin in chloroform, B, oxyhemoglobin and C, light filter 846-2.

placed in the box just behind the tubes. In either case, the solutions appear as blue to green, depending on the amount of the yellow pigment present.

In table 3 we show the effectiveness of comparing solutions through these filters. Column 1 shows the icterus index of the saline dilutions of the serum, column 2 the icterus index of the different dilutions with the addition of three drops of the solution of hemolyzed blood, column 3 the indexes read through filter 846-2, and column 4, the indexes read through filter 47.

There appears to be little choice between these two filters except in the upper ranges, where with the dark solutions the greater density of no. 47 is a disadvantage. It will be noted that in every case in which hemolysis had increased the icterus index reading, the filters have

restored it almost to normal and at the same time have not changed the readings which had not been increased by hemolysis. These filters have a definite but limited value. We strongly advise against the attempt to read the icterus index of any serum showing grossly evident hemolysis.

SUMMARY AND CONCLUSIONS

1 The solubilities and spectrophotometric qualities of bilirubin in various solvents have been studied.

2 Various solutions of potassium dichromate are compared with solutions of purified bilirubin dissolved in serum. It was found that an

TABLE 3—*Icterus Indexes of Various Dilutions of Jaundiced Serum Before and After Addition of 3 Drops of Hemolyzed Blood Read With and Without Filters*

| Icterus Index of Serum | Serum Plus 0.021% Hemoglobin | Filter Number 846-2 | Filter Number 47 |
|---------------------------|---------------------------------|------------------------|---------------------|
| 4-5 | 4-5 | 4-5 | 4-5 |
| 7-8 | 10-12 | 7-8 | 7-8 |
| 8-10 | 12-15 | 10-12 | 10-12 |
| 12-15 | 25 | 12-15 | 12-15 |
| 15 | 23-35 | 15 | 15 |
| 15-20 | 35-50 | 20-25 | 20-25 |
| 20-25 | 50 | 25-35 | 25-35 |
| 25-35 | 75 | 35-50 | 35-50 |
| 35-50 | 75-100 | 50 | 50 |

Bold faced figures denote the nearest index

icterus index of 100 matches roughly a synthetic jaundiced serum containing 100 mg. of bilirubin per liter and that weaker dilutions are nearly proportional.

3 In an attempt to remove the turbidity of jaundiced serum by the addition of alcohol-acetone mixture, it is frequently found that from 60 to 75 per cent of the bilirubin is precipitated.

4 It is shown that amounts of hemolysis which cannot be detected by the eye greatly increase the icterus index readings unless a light filter is used.

5 With specific blue color filters it is possible to determine fairly accurately the icterus index of serums containing a relatively large amount of hemolysis.

URINARY PROTEINS NOT ORIGINATING IN BLOOD

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KARL W SCHLEGEL

AND

EDMUND ANDREWS, M D

CHICAGO

The origin of the albumin in the urine is intimately concerned with the fundamental metabolic disturbances of nephritis. Immunologic studies of these proteins have thus far proved almost totally unproductive on account of the fact that serum proteins are usually present in albuminurias, and the separation of this blood serum fraction has thus far proved impossible.

Aside from the Bence-Jones protein which is probably not concerned in the problem of nephritis, pure urinary proteins have only been prepared in a few isolated cases in which crystallization took place. Such cases have been reported by Paten,¹ Bayne-Jones² and Hektoen, Kretschmer and Welker,³ and a large series of cases by Welker, Thomas and Hektoen.⁴ Excretion of protein-containing urine free from blood proteins has never been reported. In the cases quoted, the workers were unable to extract any proteins from tissues which reacted with antisera prepared for the urinary proteins.

The surest method of identification of the proteins is the immunologic technique already made use of by Hektoen and Welker.⁵ Rabbits are sensitized by the injection of blood proteins, and their sera will show positive precipitin reactions in dilution of 1 to 500,000 to this protein. Except as stated before, it has hitherto been impossible to prepare pure urinary proteins free from serum proteins, and therefore these immunologic methods have failed to identify their sources.

1 Bramwell, B, and Paten, D N. On a Crystalline Globulin Occurring in Human Urine, Reports of Lab Roy Coll Phys, Edinburgh, vol 4, pp 4, 7 and 1092.

2 Bayne-Jones, S, Wilson, D W, and Everett, H S. Precipitin Reactions of Crystalline Globulin from Human Urine, Bull Johns Hopkins Hosp **34** 77 (July) 1923.

3 Hektoen, Ludvig, Kretschmer, H L, and Welker, W H. A Peculiar Crystalline Protein in Human Urine, J A M A **83** 1154 (Oct 11) 1924.

4 Welker, W H, Thomas, W H, and Hektoen, Ludvig. Urinary Proteins—Crystalline Proteins of Nephritis, J A M A **86** 1333 and 1334 (May 1) 1926.

5 Hektoen, Ludvig, and Welker, W H. The Precipitin Reaction of Fibrinogen, J A M A **85** 434 and 435 (Aug 8) 1925.

In a previous report, one of us (Andrews)⁶ showed that the characteristic uremic syndrome can be produced by the injection of hypertonic salt solutions into animals made acid by the absorption of autogenous edema fluid. The clinical, chemical and histologic picture of uremia is accurately reproduced by this experimental method. In these experiments profound pathologic changes in the liver cells were noted, a chloride concentration higher in the liver than in the other organs, and evidence of the presence of an extreme distortion of the calcium-potassium ratio. It was suggested that as a result of a great increase

TABLE 1—*Proteins in Urine of Dog in Uremia (Whole Urines)*

| Experiment | Protein | | Precipitin Reaction—Serum 1,500,000 | | | | | | | |
|------------|------------------|-----------|-------------------------------------|------|------|-------|---------|----------|-----------|-----------|
| | Biuret or Heller | Benzidine | Undiluted | 1 10 | 1-50 | 1 100 | 1 1,000 | 1 50,000 | 1 100,000 | 1 500,000 |
| 1 A | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| B | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| C | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| D | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| E | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 A | + | 0 | + | + | ? | 0 | 0 | 0 | 0 | 0 |
| B | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| C | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| D | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| E | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| F | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3-A | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| B | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| C | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| D | + | 0 | + | + | + | 0 | 0 | 0 | 0 | 0 |
| E | + | 0 | + | + | + | 0 | 0 | 0 | 0 | 0 |
| F | + | 0 | + | + | + | 0 | 0 | 0 | 0 | 0 |
| G | + | 0 | + | + | + | 0 | 0 | 0 | 0 | 0 |
| H | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| I | + | 0 | + | + | + | 0 | 0 | 0 | 0 | 0 |
| 4 A | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| B | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| C | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| D | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| E | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| F | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| G | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| H | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

in the permeability of the liver cells soluble proteins were allowed to leak into the blood stream, and that they were excreted in the urine. It has also been assumed that passage of foreign proteins through the kidney epithelium will eventually bring about a leakage of serum proteins as well.

With these points in view, studies were undertaken of the proteins in the urines of dogs in artificial uremia, brought about as described by Andrews⁶. Two rabbits were sensitized to dog blood protein by the method previously described so that they reacted positively in dilutions of 1 to 500,000.

6 Andrews, Edmund. Artificial Uremia, Arch. Int. Med., to be published

The urinary proteins were obtained by catheter from female dogs. Specimens were collected at short intervals and kept separate. Heller's test on each sample was later confirmed by Biuret tests. Numerous samples were spoiled by the presence of traumatic blood as evidenced by positive benzidine tests. Table 1 is a summary of those results in specimens which were blood-free and still gave strong protein reactions. The negative precipitin reactions, even undiluted in some cases, showed

TABLE 2—*Proteins in Urine of Dog in Uremia (1 Per Cent Solution of Purified Proteins)*

| Experiment | Protein | | Precipitin Reaction—Serum 1,500,000 | | | | | | | |
|------------|------------------|-----------|-------------------------------------|------|------|-------|---------|----------|-----------|-----------|
| | Biuret or Heller | Benzidine | Undiluted | 1 10 | 1 50 | 1 100 | 1 1,000 | 1 50,000 | 1 100,000 | 1 500,000 |
| A | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| B | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| C | + | 0 | ?? | ? | 0 | 0 | 0 | 0 | 0 | 0 |
| D | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| E | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |

TABLE 3—*Proteins in Urines of Dogs Under Ether Anesthesia*

| Dog | Time | Heller or Biuret | | Precipitin Reaction—Serum 1,500,000 | | | | | | | |
|-----|-------|------------------|-----------|-------------------------------------|------|------|-------|---------|----------|-----------|-----------|
| | | Biuret | Benzidine | Undiluted | 1 10 | 1 50 | 1 100 | 1 1,000 | 1 50,000 | 1 100,000 | 1 500,000 |
| B | 1 30 | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2 40 | Trace | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 00 | Trace | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 20 | Trace | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| A | 2 10 | ++ | + | + | + | + | + | + | 0 | 0 | 0 |
| | 3 00 | ++ | + | + | + | + | + | + | 0 | 0 | 0 |
| C | 2 00 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2 30 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 00 | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 30 | ++ | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| D | 2 00 | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2 30 | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 00 | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| E | 2 00 | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2 30 | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 00 | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| F | 3 00 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 15 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 45 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| G | 3 15 | ++ | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| | 4 45 | ++ | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| H | 10 15 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 10 30 | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 |

clearly that these were not blood proteins leaking through. This applies only to the early samples. Later ones were invariably contaminated with serum proteins. Precipitin tests were negative, not only with the whole urine but also with 1 per cent solutions of purified proteins from those urines, as shown in table 2.

Next a series of similar tests made using the first samples of protein-containing urine brought about by etherization, as ether is a liver poison (table 3), shows that in this case also the earlier specimens are not blood proteins, but later blood proteins appear.

SUMMARY

These experiments demonstrate clearly that in the early stages of albuminuria a protein foreign to the blood proteins is excreted, and that after a short time the renal epithelium is rendered permeable to normal serum proteins

NOTE These studies are being continued by the preparation of rabbit serums sensitized to the blood-free urinary proteins and also to normal and uremic liver proteins, and other organ proteins, in order to ascertain, if possible, the source of the urinary proteins

Book Reviews

SEGREGATION AND AUTOGAMY IN BACTERIA A CONTRIBUTION TO CELLULAR BIOLOGY By F H STEWART, M D, Major, Indian Medical Service (Ret) Paper Boards Price, 7 shillings, 6 pence Pp 104 London Adlard & Son, Ltd

Among the most fascinating problems in the study of infectious diseases are variations in virulence To the physician, the microbiologist and the epidemiologist each new contribution to the study of microbic variation holds out the encouragement that perhaps the veils behind which the mysteries hide will be parted a little wider But little more than disappointment comes from an examination of this newest monograph Beginning essentially where Gurney Dixon left off nearly ten years ago, the author presents an analysis of variations in certain cultures of bacteria—particularly of variations associated with fermentation characteristics—which adds little of probable importance or permanent worth

By a series of ingenious arguments, the author demonstrates that certain variations in culture may be described by assuming that the variant characteristics are determined by multiple allelomorphs He then proceeds to the experimental "demonstration" of segregation and perhaps autogamic conjugation, and concludes by deducing a probable "life history" of a bacterium

It is rather a pity that a serious investigator of bacterial variation proceeds with complete indifference to the overwhelming evidences that plate colonies (no matter how many times repeated) are not necessarily pure cultures, and to the value of beginning with single cell strains Furthermore, although certain of the types of variations Dr Stewart describes are of unquestioned occurrence, there is almost complete neglect of all the recent experimental and speculative literature on "S—R" variations in bacteria with their associated variations in fermentative, morphologic, virulence, antigenic and other characteristics Wider familiarity with bacteriologic literature would probably force the author to dispense with his primary division of continuous and discontinuous, permanent and non-permanent variations (cf Philip Hadley, J Infect Dis 40 1, 1927)

The present monograph does not significantly modify the view generally held that the genetic interpretation of variations in the bacteria must await a more complete understanding of the determining factors than is now available

DISEASES OF THE SKIN By HENRY H HAZEN Price, \$10 Pp 572, with 248 illustrations, including 2 color plates St Louis C V Mosby Company, 1927

The medical student and practitioner will find in this conveniently sized work, accurate, concise, useful information regarding the more common dermatologic subjects Dermatoses of the negro are given special consideration, making the text valuable to those who have occasion to treat colored patients

Preliminary consideration is given to anatomy and physiology, etiology, symptomatology, pathology, diagnosis and general aspects of therapy Among the more timely chapters are those on general hygiene of the skin, emotional nervous disorders, carcinoma, and the public health aspects of syphilis Actinotherapy and diathermy are given attention Microscopic observations of the more common dermatoses are briefly presented throughout

The author avoids discussion of the relative merits of the terms "eczema" and "dermatitis," and employs only the latter He forsakes the dermatologists' heritage of "objective examination" by recommending history taking before examination

Owing to the size of the book, little space is devoted to antisyphilitic therapy. This phase has become so important that it is questionable whether it should be included in dermatologic texts. For instance, the author's "average course" of treatment for early syphilis contains, in the light of recent studies, too long (three months) mercurialization between courses of arsphenamine. The advantages of arsphenamine over neoarsphenamine are emphasized.

The clinical illustrations are numerous and are of convenient size, part of them are of colored patients, most of them are good and many are excellent. The drawings and photomicrographs, few in number, are of little value.

The book is not padded by a bibliography, although pertinent publications are mentioned in the text.

THE COMPARATIVE PHYSIOLOGY OF INTERNAL SECRETION By LANCELOT T HOBGEN, M A (CANTAB), D SC (LOND), Professor of Zoology in the University of Capetown. Price, \$3. Pp 148, with 37 illustrations and index. New York: The Macmillan Company, 1927.

This is a well written and critical statement of the comparative physiology of the endocrine glands. The arrangement of the material is from the point of view of systems in the body influenced by different hormones rather than the usual descriptions of syndromes following hypoactivity or hyperactivity of the glands. The sound critical attitude of the author may be indicated by the following quotations from the initial chapter headed "Chemical Co-Ordination": "In pursuing inquiry into the endocrine or supposedly endocrine function of so-called ductless glands the physiologist has no more justification for attributing a teleological significance to every chemical entity in the organism than neo-Darwinian naturalists had for ascribing utility to every member of the body." That is to say, the author clearly recognizes that the finding of substances by various chemical treatments of organs, substances that have various physiologic actions when introduced directly into the blood or under the skin, does not mean that these substances necessarily are produced by these organs and have these actions under normal conditions of life.

There are chapters on epinephrine and neuromuscular coordination, on the internal secretions as related to chromatic function, the endocrine factors in secretory processes, the endocrine factors in vasomotor regulation, the endocrine factors in metabolism and the endocrine factors in growth.

The author is especially conversant with the experimental literature on the endocrine glands in lower animals. Equal familiarity with the experimental and clinical literature on endocrines in the higher animals is, of course, a prerequisite in order to treat endocrinology in a comparative way. In most cases the author measures up to this requirement. The weakest chapter in an otherwise excellent monograph is that of the influence of the endocrines in secretory processes. Eddins' experiment on gastrin (1906) is quoted and discussed, while more conclusive experiments, especially those of Ivy, Lim, Luckhardt, Koch and Keeton are not referred to, although these experiments alter Eddins' original interpretation, if not the facts themselves.

The monograph is to be regarded as a valuable contribution to the subject of endocrinology and may be pursued with profit by all physicians interested in this field.

NERVE TRACTS OF THE BRAIN AND CORD. ANATOMY, PHYSIOLOGY, APPLIED NEUROLOGY By WILLIAM KEILLER, F R C S, Professor of Anatomy and Applied Anatomy, University of Texas. Price, \$8. Pp 456. New York: The MacMillan Company, 1927.

According to the intentions of the author this book will enable students to approach nervous diseases, thinking in terms of anatomy, physiology and pathology. The book consists of three parts: part 1 (pp 3 to 113), a laboratory

manual for the study of the central nervous system under normal and pathologic conditions based on Weigert and Marchi preparations, part 2 (pp 117 to 178), a summary of the anatomy and physiology of the nerve tracts, mainly based on newer methods of investigating the observations found at autopsy in chemical cases, and part 3 (pp 179 to 329), the more important features of the better known nervous diseases, correlating their symptomatology with anatomic, physiologic and pathologic data

Pages 333 to 436 contain a great many illustrations, and there is a large diagram showing the chief fiber tracts of the brain, brain stem and spinal cord

As a matter of fact, the book contains a vast amount of diversified knowledge. The author shows a surprisingly great familiarity with the anatomy of the central nervous system. It is therefore to be regretted that the facts are presented in such a way as to confuse even the more experienced reader. The three parts appear to the student as three books which deal to some extent with the same matter. Thus it comes about that there are many subjects discussed two and even three times, often in a similar style. Since most of the discussions are short and not detailed, one regrets that this unnecessary repetition occurs at the expense of the completeness of the representation. For instance, the physiology of the cerebellum is described in the first part on pages 21 and 22, in the second part on pages 169 and 170, and in the third part on page 261. Even if the points of view from which parts of the nervous system are considered may differ somewhat in the three parts of the book, the whole arrangement is rather confusing. Furthermore, the use of sketches and rough drawings does not seem to be the best method of illustration for a book of this type.

AFFECTIONS OF THE STOMACH By BURRILL B. CROHN, M.D., Associate Attending Physician to the Mt. Sinai Hospital, New York City. Cloth. Price, \$10 net. Pp 902, with 361 illustrations, some in colors. Philadelphia: W. B. Saunders Company, 1927.

The first 165 pages are devoted to the normal anatomy and physiology of the stomach, including a detailed description of the standard test meals and a discussion of their interpretation. The subject of gastric radiography is well handled and adequately for the use of the average general practitioner or internist, in 80 richly illustrated pages. The essential points in the gastric history as well as those of the physical examination of the patient are carefully pointed out.

The author devotes 215 pages to the classification, description and discussion of nonorganic diseases of the stomach including dyspepsia, achylia gastrica, gastroparesis, gastric manifestations of reflex origin, gastric neuroses and similar conditions. While there is much of good in these chapters on important and difficult subjects about which comparatively little has been definitely proved, many readers will probably be disappointed in them. The fault lies perhaps not so much with the author, as it does with the entirely inadequate knowledge of this whole group of subjects.

The 332 pages devoted to definite organic diseases of the stomach are by far the best in the book. Ulcer of the stomach and duodenum is carefully considered and thoroughly presented. The various types of medical and surgical treatment are described, and an attempt is made to evaluate them. The standpoint of the Mount Sinai group is given. The benign and malignant tumors of the stomach receive adequate attention, and the question of differentiating clinically between gastric ulcer and gastric carcinoma is dealt with fully. The chapter on organic syphilis of the stomach will interest many. The book ends with a discussion of herniation of the stomach through the diaphragm.

NUTRITION AND DIET IN HEALTH AND DISEASE By JAMES S MCLESTER, M D,
Professor of Medicine, Graduate School of Medicine, University of Alabama,
Birmingham, Ala Cloth Price, \$8 net Pp 783 Philadelphia W B
Saunders Company, 1927

This comprehensive treatise leaves nothing more to be desired in a book of its type Normal diets and normal nutritional requirements for adults and for children of the preschool age are thoroughly considered The feeding of infants is discussed in a special chapter by Dr McKim Marriott of Washington University, St Louis, and the feeding of surgical patients in a chapter written by Dr Barney Brooks of Vanderbilt University, Nashville

In the sections on diet in disease, the author does much more than give the various empiric diets that have been used, he discusses the nutritional, metabolic and digestive disturbances involved and then proceeds to outline their dietary correction Menus, recipes, tables and charts are numerous throughout the book, serving to enhance its value as a reference text for students and practitioners

SYNTHALIN

ITS USE IN THE TREATMENT OF DIABETES^{*}

A I RINGER, M D

S BILOON, M D

M M HARRIS, M D

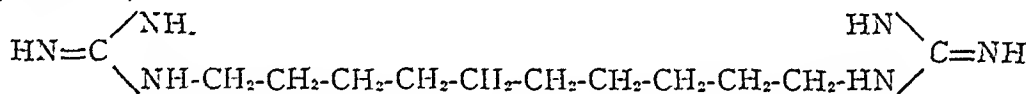
AND

A LANDY, M D

NEW YORK

Since the introduction of insulin in the treatment of patients with diabetes, various investigations have been conducted to find a remedy which would exert an influence on diabetes similar to that of insulin, but which could be administered orally

During the course of the last year, a synthetic compound named "synthalin" was developed by Frank¹ in Minkowski's clinic² in Breslau. The exact chemical composition of this substance is deca-methyl-diguanidine,



In their first communication, these authors report that they were able to reduce the blood sugar concentration in completely depancreatized dogs and rabbits by administering synthalin either subcutaneously or orally. In these animals the blood dextrose dropped from 314 mg per hundred cubic centimeters of blood to 70, and from 426 to 90. The clinical symptoms of hypoglycemia, convulsions and general paralysis, from which the animals recovered on the administration of dextrose, accompanied this drop in the blood sugar.

In their studies on diabetic patients who excreted as much as 40 Gm of dextrose a day, they report a marked drop or the disappearance of

^{*} From the Medical Division of the Montefiore Hospital

1 Frank, E., Nothmann, M., and Wagner, A. Ueber synthetisch dargestellte Körper mit insulinartiger Wirkung auf den normalen und diabetischen Organismus, *Klin Wchnschr* 5 2100, 1926, Die Synthalinbehandlung des Diabetes mellitus, *Deutsche med Wchnschr* 52 2067, 1926, *ibid* 52 2107, 1926

2 Minkowski, O. Synthetische insulinähnlich wirkende Substanzen, *Klin Wchnschr* 5 2107, 1926

the urinary sugar, ketone bodies also disappeared from the urine. The blood dextrose concentration came down to normal, and the patients were able to gain in body weight, though not as dramatically as after the administration of insulin.

They administer the drug in doses of from 20 to 25 mg twice a day on the first and third days, one dose on the second and omit it entirely on the fourth day. The reason for this procedure is that frequently after-effects develop which are due to an overdose of the synthalin. The usual symptoms caused by an overdose of synthalin are anorexia, pressure in the epigastrium, nausea and vomiting and in more severe cases, diarrhea.

In January, 1927, H. A. Metz, supplied us with synthalin that he had obtained from the Kahlbaum Company. We immediately began the studies subsequently reported.

For this study, we selected patients with diabetes of different grades of severity and those who gave the greatest promise of complete cooperation.

REPORT OF CASES

CASE 1—E. J., a girl, aged 13, had had poliomyelitis in 1918, measles in 1920, scarlet fever in 1922, chickenpox and whooping cough in 1923. In March, 1926, the patient began to have polyuria, nocturia, pruritus vulvae and loss in weight, these symptoms led to a urinary examination and to the discovery of diabetes. The patient's weight at that time was 73 pounds (33.1 Kg), the blood pressure was 120 systolic and 70 diastolic, the heart, lungs and abdomen were normal. When first examined, the urine showed a specific gravity of 1.028, dextrose, 3 per cent, albumin was not present, there was some acetone and diacetic acid. The blood sugar concentration during fasting was 195 mg per hundred cubic centimeters, the carbon dioxide capacity of the blood was 53 per cent by volume. The patient was placed on a diet consisting of 40 Gm of carbohydrate, 75 Gm of protein and 100 Gm of fat, total calories 1,360, and 18 units of insulin twice a day. On this regimen, the urine became free from sugar and ketone bodies, and the fasting blood sugar came down to 133 mg per hundred cubic centimeters.

By June, 1926, the general condition of the patient improved materially. Her weight increased to 79½ pounds (36 Kg). Her diet was increased to 75 Gm of carbohydrate, 75 Gm of protein and 150 Gm of fat. Twelve units of insulin were administered once a day. The blood sugar concentration was 133, 117 and 148 on three different examinations. On July 9, the injections of insulin were stopped. On July 29, the urinary sugar was 2 per cent, there were no ketones, and the blood sugar was 182. The injections of insulin were resumed, 14 units once a day being given. On August 25, the blood sugar was 128, and sugar was not present in the urine, on November 20, the blood sugar was 154 mg per hundred cubic centimeters, and on December 24 the blood sugar was 102. Urinary sugar was not found.

Our plan of procedure in testing the efficacy of synthalin was to stop the injections of insulin for a short period of time in order to determine the patient's ability to burn dextrose without the help of the hormone and then to substitute synthalin for the insulin.

The results of our study are tabulated in table 1. For the sake of convenience, each separate study is divided into periods. The patient's food was weighed carefully, the urine collected quantitatively and analyzed daily. The patient's weight was taken weekly, and the blood was examined at frequent intervals. Throughout the entire study, the patient was given 75 Gm of carbohydrate, 75 Gm of protein and 150 Gm of fat, she had been kept on this diet for months previous to the present study.

On January 12, the patient was given the last dose of insulin. During the first period (from January 13 to 15) insulin was not given. It is noticeable from the chart that glycosuria promptly developed, becoming more marked with each day.

During the second period (January 16 to 25) synthalin was administered as follows: two 10 mg tablets on the first day, one tablet on the second day and again two tablets on the third and fourth days, after which there was an interruption. On January 20, the patient developed epigastric distress, nausea and anorexia. By January 24, she could consume only two thirds of her diet, and even that had to be forced. The sugar in the urine cleared up, but it was difficult to decide whether the synthalin was responsible or whether this occurred because the patient had taken less food. During the third period, the feeding of synthalin was interrupted until the gastric symptoms subsided.

On January 31, the patient's condition improved so that she was able to partake of her full diet (fourth period). She developed glycosuria during those four days on full diet without synthalin. By the fourth day, she excreted as much as 31 Gm of dextrose. Her weight then was 75 pounds (34 Kg), a loss of $3\frac{1}{2}$ pounds (1.6 Kg) since the beginning of our study.

From February 4 to 20 (the fifth period), the patient was kept on synthalin and was given the full diet. The glycosuria was promptly reduced, and the gastric distress was not so marked as during the second period. She was able to partake of all her food except during one day. In spite of this, however, her body weight came down to 74 pounds (33.6 Kg), and on February 12, the blood sugar was 210 mg per hundred cubic centimeters. During the last three days of this period, she was practically sugar-free.

During the sixth period (from February 21 to 27), the synthalin was withdrawn and glycosuria promptly recurred. On February 24, ketonuria developed. On the last day of this period (February 27), the excretion of dextrose reached 25 Gm, and there was 2 Gm of acetone bodies a day. During the seventh period (from February 28 to March 11), synthalin was administered again. Glycosuria and ketonuria gradually disappeared, and the blood sugar on the last day was 138 mg. There was no further loss of body weight. Gastric distress persisted during the period at irregular intervals, but not enough to interfere with the patient's ability to consume all of her food.

During the eighth period (from March 12 to 20), the synthalin was withdrawn again. Glycosuria and ketonuria promptly reappeared, gradually increasing, so that on the last day of this period, the patient excreted as much as 1.5 Gm of ketone bodies and 31 Gm of dextrose.

During the ninth period (from March 21 to May 13), synthalin was given as indicated in table 1, every third dose being omitted. With the exception of occasional gastric distress, the patient felt well most of the time. She was able to partake of her full diet and gained in weight to 76 pounds (34.5 Kg). The urinary sugar and ketone bodies cleared up within about one week, the former reappearing on but a few occasions.

TABLE 1—Results of Study in Case 1

| Period | Date | Urine | | | | Volume, Cc | Specific Gravity | Dex. trose, Gm | Acetone and Diacetic, Gm | Nitro- gen, Gm | Diet | | | Blood Sugar, Pounds | Body Weight, Pounds | Insulin, Units | | | Synthallin, Mg | | | Remarks |
|---------|----------|----------------|-----------|-------|----|------------|------------------|----------------|--------------------------|----------------|------|----|-----|---------------------|---------------------|----------------|---|--|----------------|--|--|---------|
| | | Carbo- hydrate | Pro- tein | Fat | A | | | | | | M | P | A | | | M | P | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | |
| | 12/24/26 | | | | | | | | | | 75 | 75 | 150 | 102 | | 12 | | | | | | |
| I | 1/13/27 | 840 | 1.024 | 2 | —* | | 75 | 71 | 150 | | | | | | | | | | | | | |
| | 1/14/27 | 1,100 | 1.015 | 6 | — | | 75 | 75 | 150 | | | | | | | | | | | | | |
| | 1/15/27 | 1,500 | | 7 | — | | 75 | 75 | 121 | | | | 167 | 78½ | | | | | | | | |
| II | 1/16/27 | 1,080 | 1.024 | 14 | — | | 75 | 64 | 119 | | | | | | | | | | | | | |
| | 1/17/27 | 1,000 | 1.020 | 10 | — | | 74 | 75 | 151 | | | | | | | | | | | | | |
| | 1/18/27 | 850 | 1.032 | 15 | — | | 74 | 75 | 150 | | | | | | | | | | | | | |
| | 1/19/27 | 1,000 | 1.015 | 3 | — | | 70 | 53 | 71 | | | | | | | | | | | | | |
| | 1/20/27 | 900 | 1.020 | 4 | — | | 75 | 45 | 64 | | | | | | | | | | | | | |
| | 1/21/27 | 900 | 1.020 | 2 | — | | 52 | 44 | 68 | | | | | | | | | | | | | |
| | 1/22/27 | 832 | 1.015 | 1 | — | | 62 | 72 | 73 | | | | | | | | | | | | | |
| | 1/23/27 | 800 | 1.016 | 0 | — | | 54 | 63 | 103 | | | | | | | | | | | | | |
| | 1/24/27 | | | 0 | — | | 65 | 62 | 94 | | | | | | | | | | | | | |
| | 1/25/27 | | | 0 | — | | 65 | 60 | 78 | | | | | | | | | | | | | |
| | III | 1/26/27 | 900 | 1.015 | 0 | — | | 65 | 75 | 128 | | | | | | | | | | | | |
| 1/27/27 | | 1,600 | 1.015 | 0 | — | | 67 | 71 | 61 | | | | | | | | | | | | | |
| 1/28/27 | | 1,700 | 1.012 | 3 | — | | 75 | 72 | 116 | | | | | | | | | | | | | |
| 1/29/27 | | 1,200 | 1.012 | 4 | — | | 75 | 71 | 115 | | | | | | | | | | | | | |
| 1/30/27 | | 1,250 | 1.017 | 10 | — | | 76 | 54 | 79 | | | | | | | | | | | | | |
| IV | 1/31/27 | 1,000 | 1.020 | 10 | — | | 75 | 75 | 150 | | | | | | | | | | | | | |
| | 2/1/27 | 1,000 | 1.020 | 14 | — | | 75 | 75 | 150 | | | | | | | | | | | | | |
| | 2/2/27 | 950 | 1.027 | 17 | — | | 75 | 75 | 150 | | | | | | | | | | | | | |
| | 2/3/27 | 1,200 | 1.034 | 31 | — | | 75 | 75 | 150 | | | | | | | | | | | | | |
| V | 2/4/27 | 900 | 1.015 | 0 | — | | 74 | 75 | 150 | | | | | | | | | | | | | |
| | 2/5/27 | 900 | 1.020 | 8 | — | | 75 | 75 | 150 | | | | | | | | | | | | | |
| | 2/6/27 | 480 | 1.018 | 0 | — | | 76 | 75 | 161 | | | | | | | | | | | | | |
| | 2/7/27 | 900 | 1.017 | 11 | — | | 64 | 51 | 130 | | | | | | | | | | | | | |
| | 2/8/27 | 1,350 | 1.013 | 8 | — | | 75 | 75 | 119 | | | | | | | | | | | | | |
| | 2/9/27 | 930 | 1.015 | 6 | — | | 75 | 75 | 132 | | | | | | | | | | | | | |
| | 2/10/27 | 1,000 | 1.014 | — | — | | 75 | 75 | 111 | | | | | | | | | | | | | |
| | 2/11/27 | 900 | 1.017 | 3 | — | | 75 | 76 | 150 | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|------|---------|-------|-------|----|------|----|----|------|-------|-------|-------|---|
| VI | 2/12/27 | 963 | 1 015 | 0 | — | 75 | 75 | 150 | 210 | 12 5 | 12 5 | Gastric distress in p m Gastric distress |
| | 2/13/27 | 1,170 | 1 020 | 4 | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 2/11/27 | 1,000 | 1 022 | 11 | — | 75 | 75 | 150 | — | — | — | |
| | 2/15/27 | 930 | 1 016 | 9 | — | 75 | 75 | 151 | 12 5 | 12 5 | 12 5 | |
| | 2/16/27 | 1,000 | 1 017 | 2 | — | 75 | 75 | 125 | 12 5 | 12 5 | 12 5 | |
| | 2/17/27 | 863 | 1 015 | 2 | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 2/18/27 | 930 | 1 018 | 0 | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 2/19/27 | 1,000 | 1 017 | 0 | — | 75 | 75 | 116 | 12 5 | 12 5 | 12 5 | |
| | 2/20/27 | 960 | 1 017 | 2 | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 2/21/27 | 1,200 | 1 018 | 6 | — | 75 | 75 | 133 | | | | |
| VII | 2/22/27 | 1,000 | 1 018 | 10 | — | 75 | 75 | 131 | | | | Gastric distress, refused supper Feels well Gastric distress, anorexia Feels better Vomited, midnight Gastric distress, nausea, diarrhea Anorexia |
| | 2/23/27 | 1,030 | 1 023 | 21 | — | 75 | 75 | 130 | 12 5 | 12 5 | 12 5 | |
| | 2/21/27 | 1,200 | 1 017 | 20 | — | 75 | 75 | 149 | 12 5 | 12 5 | 12 5 | |
| | 2/25/27 | 1,000 | 1 021 | 21 | 1 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 2/26/27 | 1,220 | 1 025 | 22 | 1 06 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 2/27/27 | 1,130 | 1 023 | 25 | 2 00 | 75 | 63 | 1 12 | 12 5 | 12 5 | 12 5 | |
| | 2/28/27 | 930 | 1 028 | 19 | 1 06 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 3/1/27 | 770 | 1 026 | 15 | 0 92 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 3/2/27 | 930 | 1 022 | 11 | 0 15 | 71 | 67 | 130 | 12 5 | 12 5 | 12 5 | |
| | 3/3/27 | 900 | 1 017 | 11 | 0 33 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| VIII | 3/4/27 | 770 | 1 015 | 7 | 0 33 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | Gastric distress, anorexia Feels better Vomited, midnight Gastric distress, nausea, diarrhea Anorexia |
| | 3/5/27 | 930 | 1 018 | 5 | 0 29 | 75 | 75 | 119 | 12 5 | 12 5 | 12 5 | |
| | 3/6/27 | 1,210 | 1 022 | 10 | 0 12 | 71 | 60 | 130 | 12 5 | 12 5 | 12 5 | |
| | 3/7/27 | 1,000 | 1 020 | 5 | 0 12 | 75 | 54 | 118 | 12 5 | 12 5 | 12 5 | |
| | 3/8/27 | 1,000 | 1 021 | 5 | — | 75 | 75 | 120 | 12 5 | 12 5 | 12 5 | |
| | 3/9/27 | 930 | 1 022 | 0 | — | 75 | 75 | 119 | 12 5 | 12 5 | 12 5 | |
| | 3/10/27 | 900 | 1 011 | 0 | — | 75 | 75 | 119 | 12 5 | 12 5 | 12 5 | |
| | 3/11/27 | 1,030 | 1 015 | 0 | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 3/12/27 | 1,000 | 1 013 | 2 | 0 21 | 75 | 71 | 101 | 7 1/2 | 7 1/2 | 7 1/2 | |
| | 3/13/27 | 1,060 | 1 017 | 1 | 0 71 | 75 | 62 | 150 | 12 5 | 12 5 | 12 5 | |
| IX | 3/11/27 | 1,060 | 1 020 | 10 | 0 73 | 75 | 65 | 150 | 74 | 74 | 74 | Gastric distress, anorexia Feels better Vomited, midnight Gastric distress, nausea, diarrhea Anorexia |
| | 3/15/27 | 1,000 | 1 022 | 16 | 0 80 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 3/16/27 | 1,000 | 1 015 | 21 | 0 19 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 3/17/27 | 960 | 1 020 | 19 | 0 83 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 3/18/27 | 1,150 | 1 022 | 19 | 12 0 | 75 | 75 | 113 | 12 5 | 12 5 | 12 5 | |
| | 3/19/27 | 1,192 | 1 026 | 21 | 0 95 | 75 | 75 | 121 | 12 5 | 12 5 | 12 5 | |
| | 3/20/27 | 1,256 | 1 025 | 31 | 1 57 | 75 | 60 | 122 | 12 5 | 12 5 | 12 5 | |
| | 3/21/27 | 1,192 | 1 020 | 27 | 0 83 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 3/22/27 | 865 | 1 020 | 7 | 0 33 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 3/23/27 | 1,192 | 1 015 | 5 | 0 20 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | |
| | 3/24/27 | 930 | 1 012 | 4 | 0 15 | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 | Nausea slight Gastric distress |
| | 3/25/27 | 1,150 | 1 020 | 5 | 0 17 | 75 | 75 | 117 | 12 5 | 12 5 | 12 5 | |
| | 3/26/27 | 1,032 | 1 015 | 2 | 0 18 | 75 | 75 | 103 | 12 5 | 12 5 | 12 5 | |
| | | | | | | | | | | | | |

* — signifies acetone absent by qualitative test, + signifies acetone present by qualitative test

TABLE 1—Results of Study in Case 1—Continued

| Period IX (cont.) | Date | Urine | | | | Acetone and Diastase, Gm | Nitro- gen, Gm | Diet | | | Blood Sugar | Body Weight, Pounds | Insulin, Units | | | Synthalin, Mg | | Remarks |
|----------------------|---------|---------------|---------------------|----------------------|-------------------|-----------------------------------|----------------------|--------------|-----|-----|----------------|---------------------------|-------------------|---|------|------------------|------|------------------|
| | | Volume, Cc | Specific Gravity | Dex- trose, Gm | Carbo- hydrate | | | Pro- tein | Fat | A | | | M | P | A | M | | |
| | | | | | | | | | | | | | | | | | | |
| | 3/27/27 | 1,032 | 1.017 | 3 | — | 9.6 | 75 | 66 | 136 | | | | | | 12.5 | | 12.5 | Diarrhea |
| | 3/28/27 | 1,030 | 1.015 | 3 | — | 8.7 | 75 | 76 | 150 | | | | | | — | | 12.5 | |
| | 3/29/27 | 1,000 | 1.015 | 5 | — | 8.8 | 75 | 66 | 141 | | | | | | 12.5 | | — | |
| | 3/30/27 | 1,000 | 1.012 | 3 | — | 8.5 | 76 | 75 | 150 | | | | | | — | | 12.5 | |
| | 3/31/27 | 1,000 | 1.014 | 3 | — | 8.8 | 75 | 75 | 150 | | | | | | 12.5 | | 12.5 | |
| | 4/1/27 | 1,100 | 1.014 | 0 | — | — | 75 | 75 | 112 | | | | | | — | | 12.5 | |
| | 4/2/27 | 930 | 1.015 | 0 | — | — | 74 | 74 | 95 | | 74½ | | | | 12.5 | | 12.5 | Anorexia |
| | 4/3/27 | 1,000 | 1.014 | 0 | — | — | 75 | 58 | 128 | | | | | | — | | 12.5 | |
| | 4/4/27 | 1,000 | 1.011 | 0 | — | — | 76 | 61 | 125 | | | | | | 12.5 | | 12.5 | |
| | 4/5/27 | 1,000 | 1.011 | 0 | — | — | 75 | 75 | 133 | | | | | | — | | 12.5 | Gastric distress |
| | 4/6/27 | 1,000 | 1.015 | 0 | — | — | 75 | 75 | 137 | | | | | | 12.5 | | 12.5 | |
| | 4/7/27 | 1,000 | 1.016 | 0 | — | — | 75 | 76 | 150 | | | | | | — | | 12.5 | |
| | 4/8/27 | 1,000 | 1.012 | 0 | — | — | 75 | 75 | 94 | 173 | | | | | 12.5 | | 12.5 | Nausea, diarrhea |
| | 4/9/27 | 1,000 | 1.015 | 0 | — | — | 75 | 59 | 123 | | | | | | — | | 12.5 | Nausea |
| | 4/10/27 | 1,032 | 1.015 | 0 | — | — | 75 | 75 | 150 | | | | | | — | | 12.5 | Feels well |
| | 4/11/27 | 1,120 | 1.011 | 1 | — | — | 75 | 75 | 150 | | | | | | — | | 12.5 | |
| | 4/12/27 | 1,000 | 1.017 | 5 | — | — | 76 | 75 | 149 | | | | | | — | | 12.5 | |
| | 4/13/27 | 1,000 | 1.017 | 5 | — | — | 76 | 75 | 118 | | | | | | — | | 12.5 | |
| | 4/15/27 | 1,000 | 1.015 | 0 | — | — | 75 | 75 | 132 | | | | | | 12.5 | | — | |
| | 4/16/27 | 1,032 | 1.012 | 0 | — | — | 75 | 75 | 122 | | | | | | 12.5 | | 12.5 | |
| | 4/17/27 | 1,120 | 1.016 | 0 | — | — | 75 | 65 | 128 | | | | | | — | | 12.5 | |
| | 4/18/27 | 1,320 | 1.016 | 5 | — | — | 75 | 75 | 150 | | | | | | 12.5 | | — | |
| | 4/19/27 | 1,064 | 1.015 | 4 | — | — | 75 | 75 | 144 | | | | | | 12.5 | | — | |
| | 4/20/27 | 920 | 1.012 | 2 | — | — | 75 | 75 | 150 | | | | | | 12.5 | | 12.5 | |
| | 4/21/27 | 1,000 | 1.012 | 0 | — | — | 75 | 75 | 150 | | | | | | — | | — | |
| | 4/22/27 | 1,000 | 1.014 | 0 | — | — | 75 | 75 | 113 | | | | | | 12.5 | | 12.5 | |
| | 4/23/27 | 1,210 | 1.014 | 0 | — | — | 75 | 75 | 119 | | | | | | — | | 12.5 | |
| | 4/24/27 | 1,120 | 1.017 | 0 | — | — | 75 | 76 | 126 | | | | | | 12.5 | | — | |
| | 4/25/27 | 1,064 | 1.015 | 0 | — | — | 75 | 75 | 150 | | | | | | 12.5 | | 12.5 | |
| | 4/26/27 | 1,032 | 1.012 | 0 | — | — | 75 | 75 | 150 | | | | | | — | | 12.5 | |
| | 4/27/27 | 1,032 | 1.012 | 0 | — | — | 75 | 76 | 150 | | | | | | 12.5 | | 12.5 | |
| | 4/28/27 | 1,032 | 1.012 | 0 | — | — | 75 | 75 | 123 | | | | | | 12.5 | | 12.5 | |
| | 4/29/27 | 1,030 | 1.012 | 0 | — | — | 76 | 73 | 127 | | | | | | — | | 12.5 | |
| | 4/30/27 | 1,030 | 1.012 | 0 | — | — | 75 | 75 | 150 | | | | | | 12.5 | | — | |
| | 5/1/27 | 1,050 | 1.016 | + | — | — | 75 | 75 | 150 | | | | | | 12.5 | | 12.5 | |

| | | | | | | | | | | |
|---------|-------|-------|-----|---|----|----|-----|------|------|------|
| 5/ 2/27 | 1,110 | 1 017 | ±±± | — | 75 | 75 | 190 | — | 12 5 | 12 5 |
| 5/ 3/27 | 1,110 | 1 016 | — | — | 75 | 75 | 119 | 12 5 | — | — |
| 5/ 1/27 | 1,000 | 1 015 | — | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 |
| 5/ 6/27 | 960 | 1 015 | — | — | 76 | 76 | 150 | — | — | — |
| 5/ 6/27 | 1,032 | 1 012 | — | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 |
| 5/ 7/27 | 1,000 | 1 011 | — | — | 75 | 75 | 121 | 12 5 | 12 5 | 12 5 |
| 5/ 8/27 | 1,080 | 1 015 | — | — | 75 | 67 | 150 | — | — | — |
| 5/ 9/27 | 1,000 | 1 015 | — | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 |
| 5/10/27 | 900 | 1 015 | — | — | 75 | 75 | 150 | — | — | — |
| 5/11/27 | 1,000 | 1 012 | — | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 |
| 5/12/27 | 1,030 | 1 012 | — | — | 75 | 75 | 160 | — | — | — |
| 5/13/27 | 1,000 | 1 013 | — | — | 75 | 75 | 125 | 12 5 | 12 5 | 12 5 |
| 5/11/27 | 960 | 1 011 | — | — | 75 | 69 | 111 | 190 | — | — |
| 5/16/27 | 1,180 | 1 015 | — | — | 75 | 67 | 150 | 10 | 12 5 | 12 5 |
| 5/16/27 | 1,210 | 1 016 | — | — | 75 | 75 | 150 | 10 | — | — |
| 5/17/27 | 1,120 | 1 016 | — | — | 75 | 75 | 150 | 10 | 12 5 | 12 5 |
| 5/18/27 | 1,000 | 1 017 | — | — | 75 | 75 | 150 | 10 | 12 5 | 12 5 |
| 5/19/27 | 960 | 1 017 | — | — | 75 | 75 | 150 | 10 | 12 5 | 12 5 |
| 5/20/27 | 960 | 1 017 | — | — | 75 | 75 | 150 | 10 | 12 5 | 12 5 |
| 5/21/27 | 1,100 | 1 011 | — | — | 75 | 75 | 150 | 11 | 12 5 | 12 5 |
| 5/22/27 | 1,120 | 1 016 | — | — | 75 | 70 | 139 | 11 | 12 5 | 12 5 |
| 5/23/27 | 960 | 1 018 | — | — | 75 | 71 | 150 | 11 | 12 5 | 12 5 |
| 5/24/27 | 1,000 | 1 018 | — | — | 75 | 75 | 150 | 11 | 12 5 | 12 5 |
| 5/25/27 | 1,000 | 1 018 | — | — | 77 | 81 | 150 | 11 | 12 5 | 12 5 |
| 5/26/27 | 1,040 | 1 020 | — | — | 75 | 75 | 150 | 11 | 12 5 | 12 5 |
| 5/27/27 | 925 | 1 020 | — | — | 75 | 75 | 150 | 11 | 12 5 | 12 5 |
| 5/28/27 | 1,000 | 1 020 | — | — | 76 | 75 | 170 | 78 | 12 5 | 12 5 |
| 5/29/27 | 940 | 1 021 | — | — | 75 | 75 | 170 | — | 12 5 | 12 5 |
| 5/30/27 | 1,120 | 1 015 | — | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 |
| 5/31/27 | 1,130 | 1 015 | — | — | 75 | 75 | 150 | — | — | — |
| 6/ 1/27 | 980 | 1 022 | — | — | 72 | 73 | 150 | 12 5 | 12 5 | 12 5 |
| 6/ 2/27 | 980 | 1 011 | — | — | 75 | 75 | 170 | — | — | — |
| 6/ 3/27 | 870 | 1 015 | — | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 |
| 6/ 4/27 | 800 | 1 016 | — | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 |
| 6/ 5/27 | 1,000 | 1 018 | — | — | 75 | 73 | 119 | — | — | — |
| 6/ 6/27 | 1,100 | 1 015 | — | — | 75 | 55 | 131 | 12 5 | 12 5 | 12 5 |
| 6/ 7/27 | 1,000 | 1 012 | — | — | 75 | 71 | 150 | 12 5 | 12 5 | 12 5 |
| 6/ 8/27 | 930 | 1 015 | — | — | 75 | 71 | 150 | — | — | — |
| 6/ 9/27 | 1,120 | 1 012 | — | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 |
| 6/10/27 | 940 | 1 015 | — | — | 75 | 75 | 119 | 12 5 | 12 5 | 12 5 |
| 6/11/27 | 940 | 1 015 | — | — | 75 | 75 | 150 | 160 | 12 5 | 12 5 |
| 6/12/27 | 1,040 | 1 011 | — | — | 75 | 75 | 150 | 77½ | 12 5 | 12 5 |
| 6/13/27 | 1,150 | 1 017 | — | — | 75 | 69 | 141 | — | 12 5 | 12 5 |
| 6/14/27 | 1,000 | 1 011 | — | — | 75 | 75 | 150 | 78½ | 12 5 | 12 5 |
| 7/ 7/27 | 1,030 | 1 012 | — | — | 75 | 75 | 150 | 12 5 | 12 5 | 12 5 |

During the tenth period (from May 14 to 27), synthalin was withdrawn and insulin was substituted. The reason for that experiment was to determine whether any change in tolerance had occurred during the past five months that the patient had not been given insulin. We found that doses of insulin that could keep her aglycosuric then could not do it after the period during which insulin had not been administered. Raising of the dosage of insulin to 14 units did not clear up the condition, indicating that probably the tendency of the patient's natural tolerance was downward.

From May 28 to the time this article was written (the eleventh period) the patient was receiving synthalin in 12.5 mg doses, every third dose being omitted. On this schedule she has but occasional attacks of gastric distress, and these are slight. She remains free from sugar and ketones. The last time she was examined her blood sugar was 165 mg per hundred cubic centimeters, and her body weight was 77¼ pounds (35 Kg).

CASE 2—J L, a girl, aged 13, was admitted to the hospital on Oct. 14, 1923, complaining of weakness, polyphagia and polydipsia of eight months' duration. Her weight was 73 pounds (33.1 Kg) and her fasting blood sugar, 320 mg. On a diet consisting of 25 Gm of carbohydrate, 75 Gm of protein and 100 Gm of fat and 8 units of insulin twice a day, her urine was sugar-free and acetone-free, whereas without insulin she excreted from 25 to 30 Gm of dextrose and from 4 to 6 Gm of acetone bodies a day. She was discharged from the hospital on June 29, 1924, weighing 91 pounds (41.3 Kg) and feeling much improved.

On Nov. 14, 1924, following a cold of about one week's duration, she was readmitted in impending diabetic coma. Her blood sugar was 335 mg per hundred centimeters of blood and carbon dioxide combining power, 21.2 per cent by volume. The urine contained large amounts of dextrose and acetone and a faint trace of albumin. The results of physical examination were negative except that drowsiness, Kussmaul breathing, a rapid pulse rate (120 per minute) and temperature ranging between 100 to 102 F were noted. Two days later, she was entirely free from symptoms and felt well. During this period at the hospital, the patient excreted from 10 to 15 Gm of dextrose a day on a diet of 35 Gm of carbohydrate, 75 Gm of protein, and 125 Gm of fat and the administration of 20 units of insulin twice a day. She was discharged September 5, improved, although her carbohydrate tolerance was less than during her first stay at the hospital.

On Jan. 5, 1927, the patient was readmitted in impending diabetic coma. She gave a history of general malaise for a few weeks prior to January 5, when she began to vomit, became dyspneic and drowsy, she was therefore brought to the hospital.

Physical examination revealed signs of impending diabetic coma, drowsiness, Kussmaul breathing, rapid pulse rate (140 per minute), cold extremities and a temperature of 99.2 F. Urinalysis showed the presence of large amounts of dextrose and acetone. The patient was treated with insulin, alkali, carbohydrate and forced fluids, and the next morning she was feeling better.

Throughout January, February and March, she was kept on 50 Gm of carbohydrate, 75 Gm of protein and 125 Gm of fat, and 20 units of insulin was administered twice a day. On this regimen she excreted both dextrose and ketone bodies. She therefore offered us an excellent opportunity to study the influence of synthalin on glycosuria and ketoses unaided by insulin. On January 17, she received two doses of 25 mg of synthalin and two doses of insulin of 30 and 15 units. On that day, she excreted 53 Gm of dextrose and

TABLE 2—Results of Study in Case 2

| Period | Date | Urine | | | | Diet | | Body Weight, Pounds | Insulin, Units | | | Synthalin, Mg | | | Remarks |
|--------|-----------------|------------|------------------|---------------|--------------------|----------------|----------|---------------------|----------------|---|----|---------------|---|----|----------------------|
| | | Volume, Cc | Specific Gravity | De\xtrose, Gm | Acetone Bodies, Gm | Carbo- hydrate | Pro- ten | | A | M | P | A | M | P | |
| I | 3/ 4/27 | 1,350 | 1 022 | 18 | 2 02 | 51 | 75 | 125 | 20 | | 20 | 25 | | 25 | |
| | 3/ 5/27 | 1,620 | 1 017 | 24 | 2 16 | 50 | 74 | 126 | 20 | | 20 | 25 | | 25 | |
| | 3/ 6/27 | 1,220 | 1 015 | 12 | 1 48 | 59 | 74 | 126 | 20 | | 20 | — | | — | |
| | 3/ 7/27 | 1,400 | 1 021 | 23 | 2 49 | 51 | 71 | 126 | 20 | | 20 | 25 | | 25 | Vertigo at noon |
| | 3/ 8/27 | 1,630 | 1 021 | 29 | 3 01 | 50 | 75 | 125 | 20 | | 20 | 25 | | 25 | |
| | 3/ 9/27 | 1,690 | 1 018 | 24 | 2 07 | 50 | 74 | 125 | 20 | | 20 | 35 | | 35 | |
| | 3/10/27 | 1,620 | 1 016 | 17 | 1 34 | 51 | 75 | 124 | 20 | | 20 | 35 | | 35 | Vomited breakfast |
| | 3/11/27 | 1,520 | 1 015 | 14 | 1 00 | 50 | 75 | 125 | 20 | | 20 | 35 | | 35 | |
| | 3/12/27 | 1,560 | 1 017 | 20 | 0 79 | 50 | 76 | 124 | 20 | | 20 | 35 | | 35 | |
| | 3/13/27 | 1,680 | 1 014 | 11 | 0 65 | 51 | 75 | 125 | 20 | | 20 | 35 | | — | Vomiting |
| | 3/14/27 | 1,600 | 1 011 | 8 | 0 75 | 49 | 75 | 125 | 20 | | 20 | — | | — | |
| | 3/15/27 | 1,150 | 1 021 | 39 | 1 99 | 51 | 74 | 126 | 20 | | 20 | 25 | | 30 | |
| | 3/16/27 | 1,270 | 1 021 | 21 | 1 40 | 45 | 74 | 125 | 20 | | 20 | 30 | | 30 | |
| | Average per day | | | 20 | | | | | | | | | | | |
| II | 3/17/27 | 1,000 | 1 019 | 23 | 0 71 | 51 | 74 | 126 | 20 | | 20 | | | | Vertigo in afternoon |
| | 3/18/27 | 1,330 | 1 019 | 36 | 0 62 | 51 | 75 | 125 | 20 | | 20 | | | | |
| | 3/19/27 | 1,560 | 1 024 | 44 | 1 61 | 50 | 74 | 126 | 20 | | 20 | | | | |
| | 3/20/27 | 1,400 | 1 021 | 33 | 1 46 | 50 | 75 | 125 | 20 | | 20 | | | | |
| | 3/21/27 | 1,280 | 1 024 | 40 | 2 40 | 51 | 74 | 126 | 20 | | 20 | | | | |
| | 3/22/27 | 1,370 | 1 023 | 13 | 3 65 | 50 | 75 | 125 | 20 | | 20 | | | | |
| | Average per day | | | 36 | | | | | | | | | | | |
| III | 3/23/27 | 1,620 | 1 023 | 56 | 1 98 | 50 | 75 | 125 | 20 | | 20 | — | | 35 | Vertigo in afternoon |
| | 3/24/27 | 1,530 | 1 025 | 39 | 2 81 | 51 | 75 | 124 | 20 | | 20 | 25 | | 20 | |
| | 3/25/27 | 1,480 | 1 022 | 37 | 0 94 | 50 | 75 | 125 | 20 | | 20 | 30 | | 30 | |
| | 3/26/27 | 1,230 | 1 016 | 9 | 0 44 | 50 | 76 | 124 | 20 | | 20 | 30 | | 30 | |

234 Gm of acetone bodies in the urine On January, 18, she received only 30 units of insulin and 25 mg of synthalin twice a day On January 19, she received synthalin in two 25 mg doses but no insulin in the morning On that day, she excreted 85 Gm of dextrose and 118 Gm of ketone bodies Her general clinical condition looked unsatisfactory, and we decided to resume the injections of insulin For this reason, she was kept on both insulin and synthalin throughout February and March, when the study reported in table 2 was carried out

Because of the greater severity of the condition, this patient ran a much more uneven course as far as glycosuria and ketonuria are concerned, and from the strictly experimental point of view, this case was not as suitable or

TABLE 3—Results of Study in Case 3

| Period | Date | Urine | | | Diet | | | Synthalin, Mg | | |
|--------|-----------------|---------------|---------------------|-----------------|-------------------|--------------|-----|------------------|----|-------|
| | | Volume, Cc | Specific Gravity | Dextrose, Gm | Carbo- hydrate | Pro- tein | Fat | Sugar | A | M P M |
| I | 2/11/27 | 1,335 | 1 021 | 20 | 99 | 75 | 150 | | | |
| | 2/12/27 | 1,800 | 1 015 | 13 | 101 | 75 | 150 | | | |
| | 2/13/27 | 1,800 | 1 015 | 13 | 100 | 75 | 150 | | | |
| | 2/14/27 | 1,500 | 1 022 | 30 | 99 | 75 | 150 | | | |
| | 2/15/27 | 1,900 | 1 018 | 19 | 100 | 75 | 149 | | | |
| | 2/16/27 | 1,400 | 1 026 | 37 | 101 | 76 | 151 | | | |
| | 2/17/27 | 1,500 | 1 021 | 22 | 99 | 75 | 151 | | | |
| | 2/18/27 | 1,525 | 1 018 | 14 | 100 | 74 | 149 | | | |
| | Average per day | | | 21 | | | | | | |
| II | 2/19/27 | 1,400 | 1 019 | 7 | 100 | 75 | 150 | | 25 | 25 |
| | 2/20/27 | 1,400 | 1 017 | 8 | 100 | 76 | 150 | | 25 | — |
| | 2/21/27 | 2,300 | 1 015 | 11 | 100 | 75 | 149 | | — | 25 |
| | 2/22/27 | 1,500 | 1 012 | 8 | 100 | 76 | 151 | | 25 | 25 |
| | 2/23/27 | 1,250 | 1 018 | 6 | 100 | 75 | 150 | | — | 25 |
| | 2/24/27 | 1,800 | 1 015 | 15 | 100 | 76 | 151 | | 25 | 25 |
| | 2/25/27 | 1,425 | 1 012 | ft tr | 99 | 75 | 150 | | — | 25 |
| | 2/26/27 | 1,150 | 1 015 | 6 | 101 | 75 | 150 | | 25 | 25 |
| | 2/27/27 | 1,150 | 1 019 | 9 | 100 | 75 | 150 | | 25 | — |
| | Average per day | | | 8 | | | | | | |
| III | 2/28/27 | 1,600 | 1 020 | 29 | 99 | 75 | 150 | | | |
| | 3/ 1/27 | 1,675 | 1 020 | 28 | 100 | 75 | 149 | | | |
| | 3/ 2/27 | 1,400 | 1 021 | 22 | 101 | 64 | 148 | 184 | | |
| | 3/ 3/27 | 1,675 | 1 029 | 67 | 99 | 75 | 151 | | | |
| | 3/ 4/27 | 1,700 | 1 021 | 27 | 100 | 74 | 149 | | | |
| | 3/ 5/27 | 1,200 | 1 023 | 37 | 100 | 75 | 150 | | | |
| | 3/ 6/27 | 1,500 | 1 027 | 48 | 100 | 75 | 150 | | | |
| | Average per day | | | 37 | | | | | | |

as convincing as the first, but sufficient corroborative evidence can be gathered from it She was able to take larger doses of synthalin than the patient in case 1 without developing any marked gastric distress

During the first period, which lasted from the 4th to the 16th of March, she received 20 units of insulin twice a day and 25 mg of synthalin twice a day, as recorded in the chart Throughout the whole period, glycosuria and ketonuria persisted During the second period (from March 17 to 22), the synthalin was withdrawn During the third period, the synthalin was added again The results here can be judged only in a comparative way

The total amount of sugar excreted during the first period of thirteen days of insulin plus synthalin therapy was 261 Gm, or 20 Gm a day, whereas during the second period, the sugar excreted in six days on the same diet and insulin but without synthalin was 216 Gm or 36 Gm a day

In the third period, the synthalin was added again, and we noticed a marked drop in the glycosuria and ketonuria, unfortunately, the study had to be prematurely interrupted because the patient left the hospital

CASE 3—D K, a man, aged 39, had had diabetes for nineteen years, the last five of which had been spent in our service at the hospital. The course of his diabetic condition had always been comparatively mild. Glycosuria and hyperglycemia could be controlled by placing him on a diet of 75 Gm of carbohydrate, 75 Gm of protein and 150 Gm of fat, without the aid of insulin.

On a diet of 100 Gm of carbohydrate, 75 Gm of protein and 150 Gm of fat, he developed glycosuria, which could be controlled by 10 units of insulin administered twice a day.

The study in his case is divided into three periods and is recorded in table 3. During the first period (from February 11 to 19), he was kept on a diet consisting of 100 Gm of carbohydrate, 75 Gm of protein and 150 Gm of fat, without insulin. On this diet, he excreted 168 Gm of dextrose, or 21 Gm a day, throughout the period of eight days.

During the second period (from February 19 to 28), he received synthalin in 25 mg doses, as indicated in table 3. During this period of nine days, he excreted 70 Gm of dextrose, or 8 Gm a day.

During the third period (from March 1 to 7), the synthalin was withdrawn and glycosuria became much more marked. He excreted 258 Gm in the seven days, or 37 Gm a day.

CASE 4—S G, a woman, aged 53, had had diabetes for six years prior to admission to the hospital, during which period she lost 50 pounds (22.7 Kg) in weight. On admission, the blood sugar concentration was 293 mg per hundred cubic centimeters. Throughout the entire study, the patient was kept on a diet consisting of 75 Gm of carbohydrate, 75 Gm of protein and 150 Gm of fat.

During the first period (from March 26 to 29), she was placed on a standard diet and was found to excrete an average of 26 Gm of dextrose a day.

During the second period (from March 30 to April 13), the patient was given synthalin as described in table 4. During the first four days, there was practically no effect on the excretion of dextrose, but, beginning with the fifth day, the output dropped considerably and stayed low throughout the entire period. The average output of dextrose, not including the first four days, was 9 Gm a day (including the four days the average output was 13 Gm a day).

During the third period (from April 14 to 20), the synthalin was withdrawn. On the third day, there was a considerable rise in the excretion of dextrose which on the last day reached the highest figure, 35 Gm. The average daily output was 24 Gm, which corresponds closely with that of the foreperiod.

During the fourth period (from April 20 to May 1), synthalin was administered again. The excretion of dextrose decreased immediately and remained lower throughout the entire period. The average excretion of dextrose was 11 Gm a day.

From May 2 to 9 (the fifth period), the synthalin was again withdrawn, and the excretion of dextrose rose to an average output of 28 Gm.

CONCLUSIONS DRAWN FROM THE FOUR CASES STUDIED

The four cases studied fairly represent all stages of severity in uncomplicated diabetes. Cases 3 and 4 were comparatively mild, case 1, moderately severe and case 2 very severe. The results obtained in these cases may be discussed from the physiologic and clinical aspects.

[illegible]

Physiologic Results—Effect of Synthalin on Glycosuria The study of the influence of any drug on the sugar output in the urine must be made with the full realization that the results are of value only if we know what the food intake is, and that the patient has continued on the same diet before and after the drug has been administered, so that we have a fore and after period The sugar output in the urine in all diabetic patients represents the difference between the tolerance and the dextrose-forming material ingested In all of our cases, careful attention was paid to the maintenance of a standard diet throughout the tests, to the patient's consumption of all of the food given and to proper control periods before and after the administration of the synthalin

An analysis of the tables shows that synthalin is capable of reducing the sugar output in the urine in all the cases that we studied The patient in case 1 received synthalin during the second fifth, seventh ninth and eleventh periods, the last period extending to the date this article was written During the early periods, this patient suffered considerable gastro-intestinal distress, which manifested itself by pressure in the epigastrium after meals, anorexia, nausea, vomiting and diarrhea Because of these symptoms the patient could not consume all of her food and that in itself might have been sufficient to cause a drop in her urinary sugar But in the later periods, when gastric disturbances did not occur, the results are cleancut and convincing The results during the fifth, seventh, ninth and eleventh periods can be ascribed only to synthalin therapy Since May 28, the patient has excreted traces of sugar only occasionally being free from sugar most of the time

Cases 2 3 and 4 corroborate the observations in case 1 in that during the periods when synthalin was administered there was diminution in the excretion of sugar

Influence of Synthalin on Blood Sugar Concentration In their first communication Frank, Nothmann and Wagner¹ report their experiment on a normal rabbit in which the subcutaneous administration of 3 mg of synthalin per kilogram of body weight produced a drop in the blood sugar from 131 to 57 mg Oral administration of 50 mg to a fasting rabbit weighing 1 Kg, caused a drop in the blood sugar from 159 to 70 mg and hypoglycemic symptoms, which were counteracted by the injection of dextrose

We repeated those experiments on normal rabbits, and the following results were obtained

PROTOCOLS

RABBIT 1—This animal weighed 2.5 Kg The blood sugar was 120 mg per hundred cubic centimeters after fasting for eighteen hours

11 30 a. m One hundred milligrams of synthalin was given by mouth

4 30 p m The blood sugar was 77 mg

6 10 p m The animal looked sick Ten cubic centimeters of 16 per cent dextrose solution was given intravenously In a few minutes, the animal appeared better

Midnight The animal was found dead in its cage

RABBIT 2—This animal weighed 285 Kg

11 10 a m The fasting blood sugar was 157 mg per hundred cubic centimeters One hundred milligrams of synthalin was given by mouth

3 15 p m The blood sugar was too low to make a determination The animal appeared limp, 10 cc of dextrose was given intravenously, recovery resulted

6 10 p m The animal again appeared limp

6 30 p m Ten milligrams of dextrose was given The animal improved remarkably

Midnight The animal was found dead in its cage

RABBITS 3 and 4—These animals were treated in the same way as were rabbits 1 and 2, except that they received 25 mg of synthalin subcutaneously Within from four to five hours, both developed hypoglycemic symptoms, the blood sugar in the latter dropping to 51 mg Both animals had convulsions, from which they recovered after the intravenous administration of dextrose Both animals, however, ultimately died from their hypoglycemic condition

We administered synthalin to another series of rabbits, not in lethal doses, but in amounts that would correspond to therapeutic doses

RABBIT 5—This rabbit weighed 27 Kg Eighteen hours after his last meal, he had a blood sugar concentration of 125 mg per hundred cubic centimeters

Jan 26, 1927, 10 45 a m Five milligrams of synthalin was given by mouth

4 15 p m The blood sugar was 118 mg

January 27, 11 00 a m The blood sugar was 123 mg

Midnight Ten milligrams of synthalin was given by mouth

11 00 p m The blood sugar was 111 mg

January 28, 10 30 a m Thirty milligrams of synthalin was given by mouth

6 00 p m The blood sugar was 104 mg

January 29, 10 00 a m The blood sugar was 110 mg

This animal fasted throughout the entire period, in spite of this, he did not show a material drop in the blood sugar concentration

RABBIT 6—This animal weighed 27 Kg and was treated in a manner similar to that in which rabbit 5 was treated, having been given 5, 10 and 35 mg of synthalin on three successive days Its blood sugar throughout those four days was 114 Gm, 111 Gm, 111 Gm, 92 Gm, 117 Gm and 101 Gm, at the last determination

RABBIT 7—This rabbit weighed 233 Kg

Feb 17, 1927, 10 45 a m The blood sugar was 121 mg

11 30 a m Thirty-five milligrams of synthalin was given by mouth

5 00 p m The blood sugar was 125 mg

February 18, 11 00 a m The blood sugar was 63 mg The animal looked ill, and a grunting respiration was heard Ten cubic centimeters of 10 per cent dextrose solution was given intravenously The animal improved

RABBIT 8—This rabbit weighed 22 Kg, while fasting, his blood sugar was 118 mg He was then given 35 mg of synthalin Six hours later, his blood sugar was 124 mg, and the following morning it was 76

These experiments prove that with large doses of synthalin one can bring about a definite hypoglycemic reaction, from which the animal can be made to recover temporarily by the administration of dextrose. The giving of more moderate doses (35 mg) brought about a hypoglycemic effect in two animals and failed to give any results in two others.

The influence of synthalin on the blood sugar curve was studied in a patient with mild diabetes (Mrs. D.) on our service. Table 5 shows the results.

An examination of the blood sugar curve of this patient after the administration of 25 and 50 mg of synthalin shows a drop in the blood sugar concentration to the range of normal within eight hours. In interpreting these results, however, the element of fasting must be considered.

TABLE 5—Results of Study on a Mild Diabetic Patient

| Date | Time | Blood Sugar | Synthalin | Comment |
|---------|-----------|-------------|-----------|----------------|
| 1/14/27 | 7 30 a m | 173 | 25 mg | Fasting |
| | 7 35 a m | | | |
| | 10 15 a m | 170 | | Fasting |
| | 2 10 p m | 146 | | Fasting |
| | 5 30 p m | 137 | | |
| 3/10/27 | 9 00 a m | 170 | 50 mg | Fasting |
| | 9 05 a m | | | Fasting |
| | 1 00 p m | 151 | | Fasting |
| | 5 00 p m | 117 | | Regular supper |
| 3/11/27 | 9 30 a m | 126 | | |

In the four cases that we studied at length, case 1 showed a definite reduction in the blood sugar (eighth period), though not at the same level at which it was kept when the patient received insulin.

In case 4, on the other hand, the patient did not show an appreciable change in the figures for blood sugar, although there was a difference in the dextrose output in the urine.

In summarizing we may therefore state that the effect of synthalin on blood sugar concentration is variable, probably depending on some extraneous factor.

Influence of Synthalin on Protein Metabolism The protein metabolism was studied in cases 1 and 4. During the ninth period in case 1, the total nitrogen excreted during six days was 70.8 Gm, or an average of 11.8 Gm a day. Synthalin was not given during this period. When synthalin was administered during the tenth period, the total nitrogen excreted in eleven days was 100.6 Gm or an average of 9.1 Gm a day.

During the third period in case 4, without the administration of synthalin, 53.5 Gm of nitrogen was excreted in six days, or 8.9 Gm a day. During the twelve days of the fourth period, when synthalin was administered, the patient excreted 96.6 Gm, or 8.05 Gm on an average;

whereas during the after-period of seven days when synthalin was not given, she excreted 69.9 Gm, or 9.9 Gm a day

These two cases seem to show a diminution in the nitrogen output during the period in which synthalin was administered. An explanation can probably be found in the sparing effect on the protein metabolism of the extra carbohydrate that is utilized.

Influence of Synthalin on Ketonuria That the feeding of synthalin favorably affects the course of ketonuria is demonstrated conclusively in case 1 (sixth, seventh, eighth and ninth periods). During the sixth period, when synthalin was not given, the patient developed marked glycosuria up to 25 Gm a day and ketonuria up to 2 Gm of acetone bodies. Immediately after the administration of synthalin (the seventh period) the glycosuria and ketonuria began to subside, and on the ninth day of its administration the urine became ketone-free. In the eighth period, the synthalin was withdrawn, and the ketonuria immediately returned, reaching 1.5 Gm of acetone bodies on the ninth day. The return to synthalin during the ninth period again caused its disappearance.

The effect of synthalin in case 2, though apparent, is not so dramatic as in case 1. In case 2, the condition was much more severe, and in order to free the patient entirely from ketonuria, we would probably have had to administer much larger doses than we cared to give for fear of gastric disturbance. The results in the third period are striking, and it is much to our regret that the study could not be concluded because the patient insisted on leaving for home.

Influence of Synthalin on Combustion of Dextrose in the Diabetic Patient Direct proof that synthalin causes the combustion of dextrose in diabetes can be established only by determining the respiratory quotient. It has not been done in this work. We have, however, succeeded in demonstrating the complete disappearance of glycosuria in case 1 and the diminution of the sugar output in all of the other cases. These cannot be explained on any other basis. Retention of sugar would be followed by marked hyperglycemia, which is not noticeable, on the contrary, diminution in the blood sugar is more common.

Corroborative physiologic evidence of the theory that the dextrose is burnt during the administration of synthalin can be seen from the observation that ketonuria disappeared completely (case 1) or became considerably diminished (case 2, third period). This phenomenon can be explained only on the assumption that the dextrose acted antiketogenetically during combustion. Reduction in the nitrogen output running parallel with a diminished or disappearing glycosuria during the synthalin periods lends additional support to the theory that the synthalin causes combustion of the dextrose in a diabetic patient.

CLINICAL COMMENT

In treating patients with diabetes, one must fulfill certain requirements. The patient must be given a sufficient amount of protein to enable him to maintain nitrogenous equilibrium, a sufficient amount of fat to cover the caloric requirements and enough carbohydrate to prevent the development of ketonuria.

The condition in the great majority of diabetic patients can be controlled by merely prescribing the necessary amount of food required. In the more severe cases, this can be accomplished only with the aid of insulin. There are a large number of patients in this category who would rather have moderate hyperglycemia and glycosuria than submit to daily hypodermic injections of insulin. However, patients who develop ketonuria do not have any choice, they must take insulin or run the risk of acidosis and coma.

Insulin is the ideal drug for these patients because it clears up hyperglycemia, glycosuria and ketonuria, it alleviates all the symptoms of diabetes and improves the patient's nutrition and general well-being.

From the physician's point of view, insulin answers all requirements and has only one disadvantage, that of possible hypoglycemic reactions. From the patient's point of view, the necessity for frequent hypodermic injections constitutes a serious disadvantage. For this reason, the diabetic public looks with eagerness to biologic chemists for the discovery of a remedy which possesses the therapeutic effect of insulin but which can be administered more easily.

A survey of the action of synthalin in our cases seems to show that its discoverers have made a tremendous step in the right direction. This substance is capable of clearing up or diminishing glycosuria and ketonuria when administered in tablet form by mouth. This is a decided advantage from the patient's point of view. The possibility of gastric distress setting in is an annoying feature, but a survey of case 1, in which the patient was the greatest sufferer in the early stages, seems to show that there is a possibility of establishing a tolerance or immunity toward it. During the later periods, she did not complain. In cases 2, 3 and 4, serious gastric discomfort did not occur even in the beginning of the tests. In a number of other cases the use of synthalin, starting with doses of 25 mg, produced gastric difficulties which immediately discouraged the patients. Whether such sensitive people would gradually develop gastric tolerance for the drug can be determined only by further study. Patients who have objections to synthalin may therefore be advised to exercise a little perseverance before discontinuing its use.

In a recent publication Adler³ advises the administration of 0.5 Gm of a sodium salt of dehydrocholic acid, which is an oxidation compound

3 Adler. Nebenwirkungen des Synthalins, Klin. Wchnschr. 6:493, 1927

of cholic acid. This acts as a bile stimulant, and Adler claims that therefore it eliminates the unpleasant gastric disturbance after the administration of synthalin. We have not yet had an opportunity to test the efficacy of such medication, but we expect to do so shortly.

From the physician's point of view, synthalin has another disadvantage as compared with insulin, its action is not prompt. In one case, it took four days before any effect was noticeable, this characteristic precludes its being used in cases of emergency. In simple cases of diabetes in which the use of insulin is not desired, however, synthalin may be tried.

OCCURRENCE OF HYPERSENSITIVENESS OR ALLERGY IN FIVE GENERATIONS OF ONE FAMILY *

ABIGAIL ELIOT SMITH, M D
ST LOUIS

The basis of this paper is a study of the occurrence of allergic manifestations in the E Family, including the direct descendants of W G E (1) and A A E (2). The study includes observations on eighty-seven persons and five generations. Certain introductory statements should be made. The genealogical chart shows that W G E (1) was the son of first cousins and that he married the first cousin of both his parents, hence, a considerable reinforcement of inherited characters must have occurred in the f-1 generation. W G E (1), his wife, A A E (2), and his sister, C E L (0), were all hypersensitive. Information cannot be obtained concerning allergic manifestations in their parents. A A E (2) and W G E (1) had fourteen children, of whom nine died in early life. It has not been possible to obtain histories of these nine children other than the causes of death. They are therefore omitted from the numerical counts. They did not have any descendants.

The husbands and wives of the direct descendants have been used as controls, that is, a group of unselected persons, presumably of non-allergic stock.

The investigation was carried on entirely by correspondence, a questionnaire was sent for each member of a family group to the head member of that group. There were twenty-two such groups. The questionnaires were carefully and intelligently filled out in every case, about four weeks elapsed between the sending of the questionnaires and the return of the last set of answers. I have interpreted as correctly as possible the answers obtained, which formed the material for this work. This was not always easy, and errors have probably occurred in respect to both positive and negative observations.

Six well recognized forms of allergic reaction have been selected: asthma, hay-fever, vasomotor rhinitis, urticaria, angioneurotic edema and eczema.

The criteria by which the reported data have been evaluated are given in the following section.

* From the Department of Internal Medicine, Washington University School of Medicine.

CRITERIA OF EVALUATION FOR REPORTED DATA

Asthma—Asthma was not common in the E family. There were only four cases. The cases of E C E (74) and J G E (91) were mild and occurred only in connection with severe attacks of hay-fever. One severe case occurred in a child, aged 5 years, J W E (42). His mother, one of the control group was hypersensitive and was also subject to asthma. One of her other children had attacks of asthma associated with food allergy.

Hay-Fever—There were several severe cases and more mild cases of hay-fever.

Vasomotor Rhinitis—The term vasomotor rhinitis is used in referring to occasional attacks of coryza and sneezing apparently in the absence of infection. Under this classification is included a peculiar

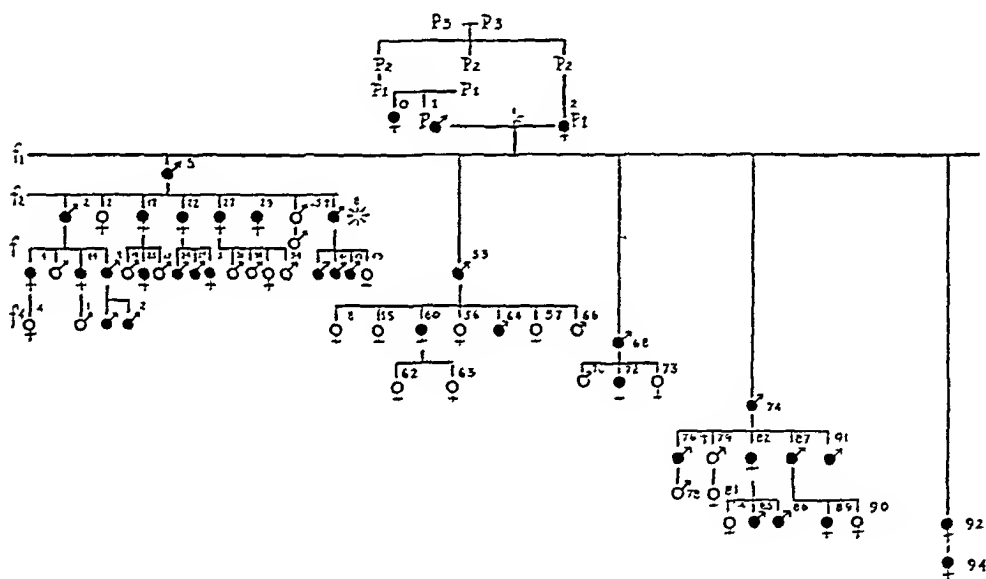


Chart 1—Cases of allergy in five generations of the E family. The hypersensitive persons are shown in black. The asterisk indicates double inheritance, the dagger, negative inheritance, in all other families one parent was hypersensitive.

manifestation which occurred in nine members of the family. This consisted of spells of sneezing, which came on without warning, any time during waking hours. R E S (92) sneezed violently from nineteen to twenty-seven times, at intervals of from thirty to forty-five seconds, with profuse nasal discharge and tearing. C R E (68) sneezed from fifteen to twenty times, and his daughter, M M E (72), sneezed from ten to twelve times. Both W G E (1) and A A E (2) had these attacks and three of their children have had them.

Urticaria—Some difficulty was encountered in making statistics of subjects with this eruption as nearly all reported that they had had "hives" or something supposed to be "hives" during their youth. I have

eliminated the doubtful cases and usually include only those attributable to some known cause. Urticaria as a sole positive symptom is used only in the case of young children with a definite history.

Angioneurotic Edema—Several interesting cases of angioneurotic edema are reported, with definite known causes.

Eczema—The infantile form of eczema had been prevalent in one branch of the family. One or two cases existed in adults.

ANALYSIS OF DATA

The collected data have been arranged in charts and tables. Chart 1 shows the five generations of the E family with the allergic members indicated. Chart 2 furnishes an analysis of the occurrence of each separate manifestation of allergy. It specially emphasizes the fact that the cases of a given form of allergy tend to occur in persons closely related, rather than at random throughout the family. Only two or three cases occurred outside the small family groups.

TABLE 1—*Numerical Summary of Cases and Analysis by Generations*

| Generation | Number of Persons | Positive Cases | Controls | Positive Controls |
|------------|----------------------|-------------------|----------|----------------------|
| P | 3 | 3 | | |
| f 1 | 5 | 5 | 5 | 0 |
| f 2 | 24 | 14 | 15 | 1 |
| f 3 | 28 | 12 | 3 | 0 |
| f 4 | 4 | 2 | | |
| Total | 64 | 36 | 23 | 1 |

Table 1 is a numerical summary of the number of persons in each generation and the number of positive cases. The distribution of the controls is shown by generations, the one positive case occurring in a person of the f-2 generation.

Table 2 is an analysis of the cases according to the presence or absence of allergy in the parents. There were two families with both parents allergic, sixteen families with one parent allergic and two with neither parent allergic.

Table 3 is a classification according to the form of clinical manifestation, showing the number of cases of each form in each generation, and the total number of each form occurring in the family.

COMMENT

Many writers express the belief that asthma is hereditary. Among the earlier authorities on this question are Cullen¹ and Andral,²

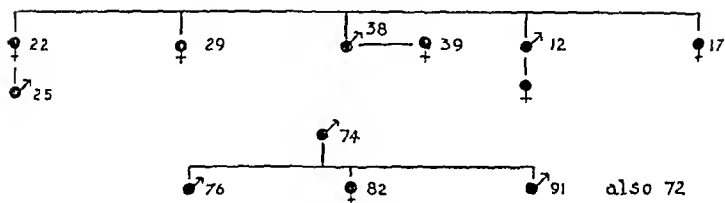
1 Cullen. Practice of Physick, ed 4, Edinburgh, 1784, p 387.

2 Andral, G. Cours de pathologie, ed 3, Brussels, 1865.

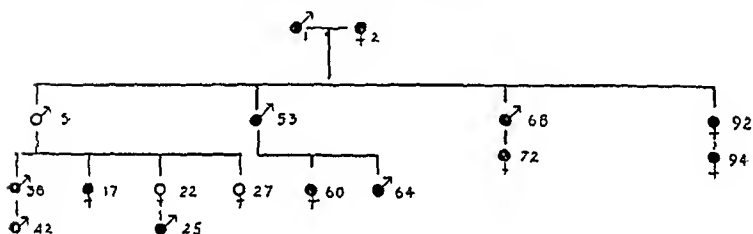
Asthma



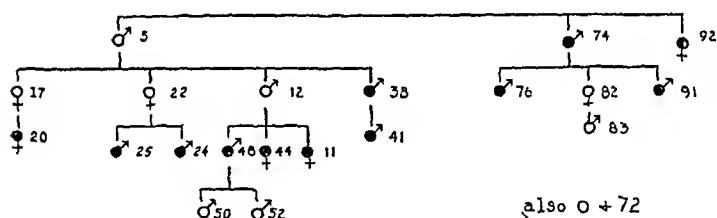
Hay=Feuer



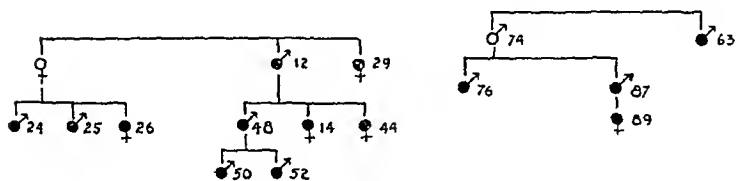
Vasomotor Rhinitis



Urticaria



Eczema



Angioneurotic Edema

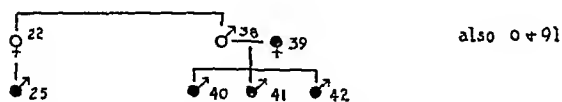


Chart 2—Showing tendency for given forms of allergic manifestation to occur in groups of persons closely related

Geddings³ in Pepper's "System," 1883, quoted Salter, Ramadge and Steavenson on the hereditary tendency in asthma. In his original description of the "exudative diathesis" with which hypersensitiveness is associated, Czerny⁴ noted the tendency of asthma to occur in families. "Protein sensitivity" was said to be hereditary by Osler, Longcope,⁵ Cooke⁶ and others.

TABLE 2—*Analysis of Cases According to Presence or Absence of Allergy in the Parents*

| Serial Number Parents | Children Double Inheritance—Both Parents Positive | Positive | Per Cent Positive |
|--|---|----------|-------------------|
| 1 and 2 | 5 | 5 | 100 |
| 38 and 39 | 4 | 3 | 75 |
| Single Inheritance—One Parent Positive | | | |
| 5 | 8 | 6 | 75 |
| 53 | 7 | 2 | 28 |
| 68 | 3 | 1 | 33 |
| 74 | 5 | 4 | 80 |
| 92 | 1 | 1 | 100 |
| 12 | 4 | 3 | 75 |
| 17 | 3 | 1 | 33 |
| 22 | 3 | 3 | 100 |
| 27 | 4 | 0 | 0 |
| 60 | 2 | 0 | 0 |
| 76 | 1 | 0 | 0 |
| 82 | 3 | 1 | 33 |
| 87 | 2 | 1 | 50 |
| 44 | 1 | 0 | 0 |
| 14 | 1 | 0 | 0 |
| 48 | 2 | 2 | 100 |
| Total | 50 | 25 | 50 |
| Negative Inheritance—Neither Parent Positive | | | |
| 79 | 1 | 0 | 0 |
| 35 | 1 | 0 | 0 |

TABLE 3—*Analysis of the Occurrence of Allergic Phenomena by Generations*

| Generation | Form of Manifestation of Allergy | | | | | |
|------------|----------------------------------|-----------|--------------------|-----------|---------------------|--------|
| | Asthma | Hay-fever | Vasomotor Rhinitis | Urticaria | Angioneurotic Edema | Eczema |
| P | | | 2 | 1 | 1 | |
| f-1 | 1 | 1 | 3 | 2 | | 1 |
| f-2 | 1 | 8 | 8 | 4 | 1 | 4 |
| f-3 | 2 | 2 | 2 | 8 | 4 | 7 |
| f-4 | | | | 2 | | 2 |
| Total | 4 | 11 | 15 | 17 | 6 | 14 |

3 Geddings. Bronchial Asthma in Pepper System of Medicine, 1883, vol 3 p 190

4 Czerny, A. Die exudative Diathese, Jahrb f Kinderh 61 199, 1905

5 Longcope W T. The Sensitivity of Man to Foreign Proteins, Harvey Lecture, 1916

6 Cooke, R A, and Vander Veer, A. Human Sensitization, J Immunol 1 201 1916

The term "hereditary" is often used by clinicians as applied to a disease which tends to appear in several members of the same family. Heredity in the biologic sense may not be involved. The study of heredity in man is a matter of considerable difficulty, and it is not certain that heredity in a human being follows the same comparatively simple laws and mechanisms that have been worked out for heredity in certain plants and lower animals. Some investigators, assuming that the mendelian laws can be applied to heredity in man, have studied the problem of hypersensitiveness from this standpoint. Drinkwater,⁷ Cooke and Vander Veer⁸ and Cooke and Spain⁸ attempted to show that sensitization to protein is a true hereditary character following mendelian principles. In an extensive study of heredity in human conditions, Buchanan⁹ failed to find evidence that asthma and "protein sensitivity" were dependent on a true hereditary factor.

According to Buchanan,⁹ in seventeen families in which one parent had asthma, 102 children did not have asthma and eight had asthma, and in thirty-six families in which neither parent had asthma, 226 children did not have asthma and forty-six had asthma. Working on the problem of hypersensitiveness to proteins, in seven families with one parent sensitive, he found thirty-six children not sensitive and two sensitive. In twenty-four families without protein sensitization in either parent, 126 children were not sensitive and twenty-eight children were sensitive. He states that if a character is hereditary, the laws of heredity must hold in 100 per cent of the cases, and that the factor either is or is not present. This is undoubtedly true as the behavior of hereditary characters is understood. But in such a condition as hypersensitiveness (which includes asthma as one of its manifestations), the difficulties in obtaining a perfect agreement with the mendelian ratios are great. The greatest care in taking histories may not result in accurate information, especially in the relatives of patients. Human families are not large enough to give a complete picture of the possible combinations of factors. Only in a large number of offspring can a close approximation to the 3:1 ratio be expected. In such a condition as hypersensitiveness to proteins there is always the possibility that a person having the factor of hypersensitiveness may not have manifested the tendency at all, or that he may have manifested it in a form which he could not recognize or remember. In young children, the factor may exist, but not show as a clinical state later in life. Cooke and Vander Veer, and Cooke and Spain

7 Drinkwater, H. Mendelian Heredity in Asthma, *Brit M J* **1** 88, 1909

8 Cooke, R. A. and Spain, W. Studies in Specific Hypersensitiveness IX. The Familial Occurrence of Hay-Fever and Bronchial Asthma, *J Immunol* **9** 521, 1924

9 Buchanan, J. A. Heredity and Human Conditions, *Am J M Sc* **165** 675, 1923

endeavored to obviate this last difficulty by estimating the number of children who would manifest hypersensitiveness at some time later in life, from certain curves based on the average age for the appearance of manifestations in different kinds of inheritance. This estimate has not been attempted in the group under consideration in this paper.

In a study of heredity in man, certain principles must be laid down as a working basis. A character which is truly hereditary is dependent on the chromosomal make-up of the germ plasma. Such a character is always associated with a contrasted character, and one is dominant over the other—that is, when genes for both characters are present in the same person, the dominant one is evident, while the other is concealed. The mendelian laws deal with the behavior of these genes. In this discussion the existence of the two characters “hypersensitive” and “not hypersensitive” has been assumed. As will be seen, it is not easy to decide which should be considered “dominant” and which “recessive.”

If “hypersensitive” is the dominant factor the following results from the six possible varieties of mating may be expected

DD × DD—offspring all hypersensitive
 DD × DR—offspring all hypersensitive
 DD × RR—offspring all hypersensitive
 DR × DR—75 per cent of offspring hypersensitive
 DR × RR—50 per cent of offspring hypersensitive
 RR × RR—no hypersensitive offspring

If “hypersensitive” is the recessive factor

DD × DD—no offspring hypersensitive
 DD × DR—no offspring hypersensitive
 DD × RR—no offspring hypersensitive
 DR × DR—25 per cent of offspring hypersensitive
 DR × RR—50 per cent offspring hypersensitive
 RR × RR—all offspring hypersensitive

Assuming that “hypersensitive” is the dominant factor, three kinds of matings can be determined in the E family

1. When both parents are hypersensitive, DD × DD, DD × DR or DR × DR are the resultant combinations. In the first two matings, one would expect 100 per cent of the children to be hypersensitive, in the third 75 per cent. Actually, one finds two families with both parents hypersensitive. The five children of W G E (1) and A A E (2) were all hypersensitive. It is improbable, however, that either W G E (1) or A A E (2) were DD because there is not any evidence of a DD parent among the members of the f-1 generation, as shown by 100 per cent hypersensitive offspring in one family of children A A E (2) and W G E (1), as well as T L E (38) and S W E (39), must represent the DR × DR type of mating. There

were nine children in these two families, eight of whom were hypersensitive. The only nonhypersensitive case occurred in a baby less than 1 year of age.

2 When one parent is hypersensitive, $DD \times RR$ or $DR \times RR$ are the resultant combinations. $DD \times RR$ probably does not occur, for reasons explained in the preceding paragraph. $DR \times RR$ gives an expectation of 50 per cent hypersensitive offspring, which is the figure obtained in the E family.

3 When neither parent is hypersensitive, $RR \times RR$ is the resultant combination. Only two such families had children. In each family there was one child and neither of the children was hypersensitive.

The observations in the E family agree well with the expected figures for a dominant factor, but the number of cases is too small for one to draw conclusions.

TABLE 4—Results in E Family with "Hypersensitive" as Dominant Factor

| Summary of Matings | Theoretically Hypersensitive | Actually Hypersensitive |
|--------------------|---------------------------------|----------------------------|
| $DR \times DR$ | 75% | 88.8% |
| $DR \times RR$ | 50% | 50% |
| $RR \times RR$ | 0 | 0 |

TABLE 5—Results in E Family with "Hypersensitive" as Recessive Factor

| Summary of Matings | Theoretically Hypersensitive | Actually Hypersensitive |
|--------------------|---------------------------------|----------------------------|
| $RR \times RR$ | 100% | 88.8% |
| $RR \times DR$ | 50% | 50% |
| $DR \times DR$ | 25% | 0 |

Assuming that "hypersensitive" is a recessive factor, the possibilities and actual observations are summarized in table 5.

Although the actual figures are not greatly at variance with the theoretical figures, it is difficult to interpret the hypersensitive factor as a recessive characteristic, because it would then be necessary to postulate a factor for "hypersensitive" in both parents whenever there is a hypersensitive child.

Table 6 gives the percentages of hypersensitive offspring obtained by Drinkwater⁷ in a family of asthmatic persons, reported in 1909. It shows also the results of Cooke and Spain in 1,889 cases reported in 1924.

The evidence from the three sets of figures seems to point to an inherited character as the basis for naturally occurring allergy, probably a dominant factor. Two points in favor of this interpretation are

1 Not all the children with two hypersensitive parents can be shown to be hypersensitive, as is necessary in case the character is recessive

2 In order to have any hypersensitive children in the case of single inheritance, if the character is recessive, it is necessary that the nonhypersensitive parent carry the recessive factor for "hypersensitive" Therefore, every one of the eleven persons who married hypersensitive members of the E family and had hypersensitive offspring must have been of hypersensitive families Only two of them had family histories of hypersensitiveness, and only one of the two was hypersensitive

The 41.1 per cent found by Cooke and Spain⁸ to be hypersensitive persons with neither parent hypersensitive cannot be reconciled with the interpretation as a dominant factor In working from a single patient to the histories of his relatives, however, it is not always possible to get accurate information, and some cases of hypersensitiveness in parents might be missed

TABLE 6—*Percentages of Positive Cases in Families Studied by Drinkwater, Cooke and Spain and of Those in the E Family*

| | Double Inheritance | Single Inheritance | Negative |
|-------------------------------------|--------------------|--------------------|----------|
| Drinkwater, 20 cases | | 50% | 0 |
| Cooke and Spain, 1,889 cases | 69.4% | 58% | 41.1% |
| E family | 88.8% | 50% | 0 |
| Expected ratio, dominant character | 100% or 75% | 50% | 0 |
| Expected ratio, recessive character | 100% | 50% | 25% |

In interpreting the hypersensitive tendency as a dominant hereditary character, I agree with Cooke and Spain,⁸ but differ with Adkinson,¹⁰ who has interpreted it as a recessive factor The 41.1 per cent of hypersensitive persons with neither parent hypersensitive favors this interpretation, as under these circumstances 25 per cent of the offspring may be expected to show the character

If the character is hereditary, as is understood in the biologic sense, either the absence of 100 per cent incidence in double inheritance or the presence of 41.1 per cent incidence in negative inheritance must be wrong, according to the conditions laid down for a true inherited character

The reasons for the discrepancies here encountered have already been discussed The conclusion, therefore, that such a character as "hypersensitive" exists but that it is dominant cannot be made However, the transmissibility of the allergic tendency from parent to child appears to be demonstrated conclusively

10 Adkinson, J Bronchial Asthma as an Inherited Character, *Genetics*, 5 365, 1920

SUMMARY

1 A family of ninety-four persons and five generations was studied by means of histories obtained through questionnaires, in regard to the hereditary occurrence of allergic manifestations. The manifestations of allergy considered were asthma, hay-fever, vasomotor rhinitis, urticaria, angioneurotic edema and eczema.

2 Twenty-three persons who were married to members of the E family have been used as controls. As a group of unselected normal patients, their histories were taken in the same manner as the histories of the E family.

3 In the E family, 56.2 per cent of the members were allergic. Among the twenty-three controls, not related to the family except by marriage, only one was allergic.

4 The results of this survey support the contention that allergy is familial in distribution.

5 Given forms of allergic manifestation apparently tend to be prevalent among closely related persons.

HEMOCIDAL PROPERTIES OF THE BLOOD SERUM

WITH SPECIAL REFERENCE TO PERNICIOUS ANEMIA

O H HORRALL, M D

CHICAGO

AND

T E BUCHMAN, M D

JACKSONVILLE, FLA

Notwithstanding the fact that increased destruction of blood in pernicious anemia was demonstrated over thirty years ago by Hunter,¹ it would appear from a careful search of the literature that a direct destructive action of the blood serum on the red corpuscles in this disease has not been demonstrated. The bulk of the research on the mechanism of erythrocyte destruction in pernicious anemia appears to have been directed toward the demonstration of a localization of the process in certain organs, especially in the bone marrow, spleen, hemolymph nodes and liver. The investigations have been carried out principally along three different lines of pursuit: (1) histologic studies of the phagocytic activity of the cells of the different organs, (2) the quantitative determination of the iron content of these organs, and (3) the isolation of hemolytic substances from these organs.

Hunter found excessive deposits of pigment in the cells of the livers of persons dying of pernicious anemia, and so convinced was he that the liver is the principal site of cell destruction, that he concluded that the causative agent of the disease must be of intestinal origin. Dickson² showed that the bone marrow is the site of extensive phagocytosis of red corpuscles, not only in pernicious anemia, but also in other severe chronic anemias and in certain acute infections associated with a leukopenia. He was of the opinion that the bone marrow is the principal site of erythrocytolysis in pernicious anemia.

In a more recent article, Schneider,³ while, of course, not denying the existence of phagocytosis in the spleen, is of the opinion from histologic studies of spleens made by him in association with Eppinger in the Von Noorden Clinic, that the actual hemolysis (escape of hemoglobin) takes place in the Kupffer cells of the parenchyma of the liver.

1 Hunter, William. Pernicious Anemia, Charles Griffin & Company, 1901, p 77, Severest Anemias, London, 1909, p 110, Brit M J 2 81, 1890, Lancet 1 287, 1890, 1 283, 1903

2 Dickson. The Bone Marrow, New York, Longmans, Green and Company, 1908, p 73

3 Schneider, J P. The Splenic Pathology of Pernicious Anemia and Allied Conditions, Arch Int Med 17 32 (Jan) 1916, Journal-Lancet 37 105, 1917

None of the investigations has disclosed anything peculiar to the phagocytosis that occurs in pernicious anemia, and Warthin⁴ concluded that cell destruction in pernicious anemia differs only quantitatively from that which occurs normally. Dickson states that the phagocytic cells of bone marrow arise from endothelial lining of blood capillaries and from adenoid reticulum of the marrow. "Pigment cells and cells containing erythroblasts and red corpuscles are seen in very great numbers in the bone marrow whenever there is any great amount of blood destruction going on in the organism. This is seen in pernicious anemia and other long-standing anemias, also seen in equal and even greater numbers in acute diseases, especially septicemias and pneumonias with leucopenia. I therefore regard the marrow as one of the principal sites of hemolytic action, scarcely, if at all of less importance, in the carrying on of this function than are the liver and spleen, a fact which is all the more striking when the great extent and the wide distribution of the red bone marrow throughout the body is borne in mind."

Warthin⁴ reported eight cases of pernicious anemia, including post-mortem examination, in which he found changes in both the lymph and hemolymph nodes which varied greatly in degree. In only one case did the peripheral glands (axillary, superficial cervical, inguinal and cubital) show any change that could be regarded as belonging essentially to pernicious anemia, also the changes in the mesenteric glands were not constant, occurring only in two cases. In all eight cases he found changes in the prevertebral, retroperitoneal and cervical lymph and hemolymph glands indicating excessive hemolysis. These changes were an apparent increase in the number and hyperplasia of resting hemolymph glands, dilatation of the blood sinuses, with an increase in the number of phagocytes containing disintegrating red cells and pigment, and in the lymph gland, dilatation of the lymph sinuses, presence of increased number of red blood cells in the latter, an increased number of phagocytes and congestion. The difference in degree of changes suggests intermittent hemolysis. In some cases, very little hemosiderin or few phagocytes containing red blood cells are found in the spleen, while they are abundant in the hemolymph glands and vice versa.

The hemolytic poison does not confine itself to the portal areas as claimed by Hunter, but is present in the general circulation. Furthermore, as pointed out by Hunter, the hemolysis of pernicious anemia is a cellular process and is performed by the phagocytes of the spleen, lymph glands, hemolymph glands and bone marrow in response to the direct stimulus of the poison or of blood cells injured by the poison. He did not find any evidence of hemolysis in the liver in his eight cases. He thinks the hemolysis of pernicious anemia does not differ in kind from that which occurs in other diseases but that the difference is one of

4 Warthin, A. S. *Am J M Sc* **124** 674, 1902, *J M Research* **7** 435, 1902.

degree only Lymphoid and megaloblastic changes in the marrow do not form an essential part of the pathologic processes in pernicious anemia and are to be regarded as of a compensatory nature—an increased activity of red blood cell formation occurs to supply the deficiency caused by the excessive hemolysis

Determinations of the iron content of the organs offer a less satisfactory source of evidence than does phagocytosis regarding the localization of the process of cell destruction, as the iron content of an organ presumably depends to some extent on the rate of utilization of iron for the purpose of manufacturing of red cells Queincke⁵ found the iron content of the liver below normal in cases of excessive loss of blood from the body, and Muir and Shaw Dunn⁶ found that the excess of iron stored in the organs of rabbits following acute anemia caused by injection of hemolytic serum was almost entirely absorbed by the time complete regeneration of blood had taken place, the absorption from the cells of the liver was almost complete, but a certain excess remained in the splenic pulp and in the renal cortex

Hunter, however, was convinced that the characteristically high values found by himself and others for iron content in the liver in pernicious anemia was evidence of a localization of the process of cell destruction in that organ Schneider interpreted the marked urobilinuria which he observed in pernicious anemia as evidence of excessive destruction of red cells in the liver Ryffel⁷ has determined the iron content in six cases of pernicious anemia In five of these cases, the liver and spleen showed a higher iron content than that found in normal cases, usually the iron content of the liver (in weight per cent) was higher than that of the spleen, kidney or heart (from 0.24 per cent to 1.01 per cent in the liver, the normal weight for the liver is about 0.10 per cent) Unfortunately, the normal weight (as they considered it) is not stated in any of their investigations

The reported results of attempts to isolate hemolytic substances from the organs in pernicious anemia have been inconsistent and difficult of interpretation This has been noted especially because (1) tissues when removed from the body, even under aseptic conditions, tend to undergo autolysis and the products of autolysis are themselves hemolytic, and (2) hemolytic substances have been isolated from fresh normal organs Robertson⁸ found that whereas alcoholic and saline extracts of

5 Queincke *Deutsches Arch f klin Med* **27** 193, 1880

6 Muir and Dunn, Shaw *J Path & Bact* **20** 41, 1915, **21** 417, 1917

7 Ryffel, J H *J Path & Bact* **14** 411, 1909

8 Robertson, O H A Study of Hemolytic Activity of the Spleen in Pernicious Anemia, *Arch Int Med* **16** 652 (Oct) 1915, Urobilin in the Stool—Urobilin in the Stool in Pernicious Anemia as Influenced by Splenectomy, Transfusion and Salvarsan, *ibid* **16** 429 (Sept) 1915, An Index to Blood Destruction, **15** 1072 (Dec) 1915, Robertson and Rous *J Exper Med* **25** 665 and 651, 1917

fresh pulp from spleens removed at operation in cases of pernicious anemia did not possess hemolytic properties, ethereal extracts possessed marked hemolytic activity, ethereal extracts of normal liver and of normal intestine also possessed hemolytic properties. Nolf⁹ found that extracts of normal spleen possess marked hemolytic activity, and Banti¹⁰ likewise reported evidence of a hemolytic substance extracted from the spleen. On the other hand, Pearce, Krumbhaar and Frazier¹¹ reported that they were unable to demonstrate any constant hemolytic properties in saline extracts of fresh spleen, mesenteric lymph nodes or liver.

Wells^{11a} said, "It is not generally accepted that the spleen plays an essential rôle in causing pernicious anemia through excessive phagocytosis or production of hemolytic poisons."

It is, however, impossible to deny that because there is no satisfactory evidence of a specific soluble hemolysin that can be isolated from the spleen in pernicious anemia, the spleen does not possess erythrocytotoxic properties other than phagocytic. Bottazzi¹² demonstrated an increased resistance of red corpuscles to hypotonic salt solution after splenectomy and suggested that the spleen acts to render the red cells more susceptible to destruction. However, direct proof of this action has not been furnished. Butler¹³ studied the resistance of the red corpuscles to hypotonic salt solution in four cases of pernicious anemia and found that they appeared to have normal values. Bigland¹⁴ did not find any abnormal fragility of the corpuscles from six cases of pernicious anemia in which tests against saponin were made, and Rous¹⁵ did not find lowered resistance of corpuscles in cases of pernicious anemia to hemolytic serum. Robertson studied the resistance of red cells taken from the splenic vein and artery in three cases of pernicious anemia in which the spleen was being removed by operation. In each case he found that the cells from the splenic vein showed a distinctly decreased resistance to hypotonic salt solution compared to those taken from the splenic artery. The resistance of the splenic venous corpuscles was less than that of peripheral venous corpuscles and less than that of normal controls. In fact, the resistance of the corpuscles from the peripheral venous blood was greater than normal in most cases. Pearce, Krumbhaar and Frazier¹¹ stated that the resistance is usually, but not always, increased in pernicious anemia.

9 Nolf, P. *Compt rend Soc de biol* **72** 121, 1912

10 Banti. *Semaine méd* **32** 265, 1912, **32** 313, 1913

11 Pearce, Krumbhaar and Frazier. *Spleen and Anemia*, Philadelphia, Lippincott & Company, 1918

11a Wells. *Chemical Pathology*, Philadelphia, W. B. Saunders Company

12 Bottazzi. *Lo Sperimentale* **68** 433, 1894

13 Butler. *Quart J Med* **6** 145, 1912

14 Bigland. *Quart J Med* **7** 370, 1913

15 Rous, P. *J Exper Med* **11** 763, 1909

In this connection, it should be borne in mind, however, that the reticulated cells may influence the fragility values. Pepper and Peet¹⁶ concluded from their own experiments and from a review of the literature that the reticulated erythrocytes show a greater resistance to hemolytic agents than do unreticulated forms. It would seem from the results of certain observations recorded in this paper that whereas the reticulated cells after hemorrhage are more resistant than the unreticulated forms tested by hypotonic salt solution, those of the reticulated cells of pernicious anemia are less resistant, and if present in sufficiently great quantities may appreciably influence the total fragility so that hemolysis will appear to begin at a higher figure, thus simulating hemolytic jaundice. As Minot¹⁷ pointed out, such cases clinically simulate hemolytic jaundice chronically acquired and are the ones in which the best results are to be expected from treatment by splenectomy.

Of a wholly different nature is the histologic evidence brought forth by Eppinger,¹⁸ who found in the spleens of patients with pernicious anemia hyaline degeneration and increased thickness of the central arteries resulting in a diminution of the caliber of the lumen. As a result of this stenosis, Eppinger concludes that an abnormally great amount of blood is forced directly into the pulp area through the capillaries of Weidenreich. In the pulp area the blood is prepared for hemolysis later to be affected by the Kupffer cells of the liver. The increased destruction of blood in pernicious anemia is thus not due to an increase in the speed with which blood is prepared for destruction.

Schneider stated "Contrary to the conception of Aldis, hemolysis occurring to the extent of allowing detection of free hemoglobin in the spleen is rare, and whether engulfed by the phagocytic endothelial cells or not, the actual hemolysis occurs in the Kupffer cells of the liver parenchyma. Pleiochromia is an expression of immediate hemolysis, urobilinocholia the heaped up pigment in the portal system." Pernicious anemia shows, both Wilbur and Aldis¹⁹ stated, that by means of estimations of urobilin in the urine and feces the forms of anemia associated with increased destruction of blood may be differentiated. Both are high in pernicious anemia.

16 Pepper, O. H. P., and Peet, N. M. The Resistance of Reticulated Erythrocytes, *Arch Int Med* **12** 81 (July) 1913.

17 Minot and Lee. *Boston M & S J* **177** 761, 1917. Minot, G. R. *Oxford Medicine*, vol 2, p 589. Lee, R. I., and Minot, G. R. *Cleveland M J* **16** 65, 1917. Minot, G. R. *Boston M & J* **174** 667, 1916. Lee, R. I., Minot, G. R., and Vincent, B. Splenectomy in Pernicious Anemia, *Studies in Bone Marrow Stimulation*, *J A M A* **67** 719 (Sept 2) 1916. Minot, G. R. *Bull Johns Hopkins Hosp* **25** 338, 1914.

18 Eppinger. *Berl klin Wchnschr* **50** 1509, 1572 and 2409, 1913.

19 Wilbur and Aldis. Urobilin. Its Clinical Significance, *Arch Int Med* **13** 235 (Feb) 1914.

Further evidence of the mechanical influence of the spleen has been brought forth by Pearce, Heitin and Eisenbrey,²⁰ who showed that jaundice persisted for a longer period in dogs when hemoglobin was injected into the mesenteric vein than when it was injected into the femoral vein. Warthin⁴ has shown that hemolysis by the hemolymph glands exceeds that found in the spleen after splenectomy. Pearce and his collaborators explained the lessened tendency to jaundice after splenectomy as due in part to the fact that the products of red cell destruction are liberated, not into the portal system, but into the general circulation. That such a mechanism may be effective in pernicious anemia is reasonable, but has not been proved.

Finally, the effects of splenectomy in pernicious anemia constitute uncertain evidence, as (1) the results are uncertain, and (2) the hemolymph glands, which are functionally similar to the spleen, may then take on the activities of the spleen. One is inclined to agree with Hirschfield²¹ that the spleen is not the essential organ in causing either the excessive phagocytosis or the increased hemolysis in pernicious anemia.

There is little evidence to show that humoral factors may play a rôle in the excessive blood destruction of pernicious anemia. Joannovics and Pick²² found in experimental phosphorus poisoning an increased amount of unsaturated fatty acids in the serum and suggested that the increased hemolysis may be due to the increased unsaturated fatty acids. Eppinger, and later King,²³ attempted to demonstrate a parallelism between the quantity of unsaturated fatty acids in the serum and the extent of hemolysis in pernicious anemia. McPhedran,²⁴ however, was unable to demonstrate any undue hemolytic action of unsaturated fatty acid *in vitro*. In fact, he concluded from his work that "hemolysis by unsaturated fatty acids is not more active in proportion to the degree to which these acids are unsaturated, nor is it diminished when unsaturated carbon atoms are saturated by halogens but is diminished when they are converted into corresponding hydroxyl acids which are hemolytic only to the same degree as saturated acids."

Interesting but unproved is the theory of Cederberg²⁵. He conceived of pernicious anemia as a manifestation of anaphylaxis caused by the passage of an incompletely broken-down foreign protein into the circulation through constitutional defects in the intestinal mucosa. This pro-

20 Pearce, R. M., and others. *J. Exper. Med.* **16**: 363 and 780, 1912.

21 Hirschfield. *Ztschr. f. klin. Med.* **87**: 165, 1919.

22 Joannovics, G., and Pick, E. P. *Ztschr. f. exper. Path. u. Therap.* **7**: 185, 1910.

23 King, J. H. *Studies in the Pathology of the Spleen*, *Arch. Int. Med.* **14**: 145 (Aug.) 1914.

24 McPhedran. *J. Exper. Med.* **27**: 527, 1913.

25 Cederberg. *Berl. klin. Wchnschr.* **51**: 585, 1914.

tein then acts in the blood stream as a hemolytic agent. He reasons from the analogy of observations on the blood of animals dying of anaphylactic shock which shows a certain amount of hemolysis.

TECHNIC OF TEST

Sufficient blood to yield about 25 cc of serum and 5 cc of red cells was obtained from the patient and the same amount from a normal person of the same iso-agglutination (isohemolytic) group, determined by the Moss method. All of the patients except two had negative Wassermann tests, and races were not crossed. The Wassermann tests were made in Dr. Mallory's laboratory. The blood specimens from which serums were obtained were placed in large test tubes and allowed to stand in the ice chest until a firm, well retracted clot had formed and the clear serum had separated. The blood specimens from which cells were obtained were defibrinated with beads, centrifugalized and the serum pipetted off, and then washed once with an 0.8 per cent solution of sodium chloride, again centrifugalized, and the supernatant fluid pipetted off. A 50 per cent suspension of these cells was made up in 0.8 per cent salt solution and placed in the ice chest. When the blood in the test tubes had clotted sufficiently well to permit the decantation of the serum, which usually took about four hours, the serum was poured off for use in the test, centrifugalized and the clot discarded. Specimens in which hemolysis had occurred were not used.

The following series of test tubes, each containing 1 cc of fluid, was then set up in duplicate: (1) salt solution, ranging in concentration from 0.6 per cent, or higher, to 0.1 per cent at intervals of 0.025 per cent, (2) normal serum, two sets, progressively diluted with distilled water, the first tube containing pure serum and each successive tube containing 0.05 cc more of distilled water and 0.05 cc less of serum than the one immediately preceding it, until a dilution of serum corresponding to 1:19 was reached, (3) abnormal serum, two sets, diluted in the same manner as the normal serum. To each tube of one of the duplicate sets in each of the three series was then added 0.1 cc of the 50 per cent suspension of washed normal cells and similarly to each tube of the other of the duplicate sets of each of the three series was added 0.1 cc of the 50 per cent suspension of the washed cells of the patient. All the tubes were then shaken in order to mix the cells and supernatant fluid and then placed in the icebox for two hours. They were then removed, again shaken, and allowed to stand at the temperature of the laboratory (about 20 C) for one hour, and then incubated for one hour at 37 C. Observations were then made. In each of the six sets of tubes the dilution at which hemolysis was observed to commence and the dilution at which hemolysis was observed to be complete were noted. Hemolysis was deemed to be complete when the color of the supernatant fluid was of the same intensity as that of a solution of normal red cells made by adding 0.1 cc of a 50 per cent suspension of such cells to 1 cc of distilled water. Dilutions of normal and of abnormal serum with distilled water were then made up corresponding to those dilutions at which hemolysis was observed to commence and at which hemolysis was observed to be complete in the case of the normal cells and of the patient's cells. The freezing point depressions of these diluted serums were then determined by means of the Beckmann thermometer in the usual manner. From tables in Landolt and Bornstein's "Compendium," the percentage concentrations of salt solutions corresponding to these freezing point depressions were ascertained. It was deemed more convenient to express all dilutions in terms of equivalent percentage concentration of sodium chloride than in terms of freezing points,

merely because it is conventional to express the results of fragility tests in terms of percentage of concentration of sodium chloride. For this purpose, it is convenient to construct from the standard tables a curve showing the relationship of concentration of sodium chloride to the depression of the freezing point.

A complete record of history, physical observations, laboratory and roentgen-ray reports was made, as all these patients were admitted to the hospital for research. In addition, the following special tests were made: hematocrit, serum color, differential red counts, reticulated red counts, differential white counts, platelets, hemoglobin, color index, coagulation time, bleeding time, blood group—Moss method and Wassermann.

COMMENT

Practically all the tests for fragility of the red blood cells have been made with hypotonic salt solution. A few reports have been made of tests in which saponin and bile have been used. In the composite chart in which the data for abnormal cells in salt solution is shown, the extreme variations for the beginning of hemolysis is 0.51 for hemolytic jaundice and polycythemia to 0.38 for pernicious anemia in remission taken by group. When individual cases are considered, the maximum is 0.65 in a case of undiagnosed anemia (at first thought to be pernicious anemia) to 0.35 in aplastic anemia. These ranges are rather striking when only a few cases are considered, but, when the groups are compared to the normal, which is 0.404, most of the groups appear to have slightly increased fragility for the beginning of hemolysis. The completion of hemolysis in salt solution for the normal is 0.29 while the extremes by groups is 0.27 for pernicious anemia in relapse and septic anemia and 0.19 for polycythemia, in individual cases, 0.35 for pernicious anemia in remission and 0.12 for polycythemia. When the behavior of the cells in salt solution alone is considered, a few cases stand out strikingly, but when groups are considered such definite characteristics cannot be observed, and conclusions cannot be drawn which will make the test of value in diagnosis.

The fragility of the red cells may depend on a number of things:

- 1 The most fragile cells may have been destroyed in the body before the blood was taken, and when the test is made only the more resistant cells are available.

- 2 If the severe destruction has taken place several days prior and enough time has elapsed for young cells to be thrown into the circulation in quantities sufficient to influence the test, the resistance of young cells will be tested. Reticulated red cells appear to react normally to salt and serum (chart 1).

- 3 If the destruction has been gradual over a long period of time and the replacement has appeared at the same rate, a rather wide range of fragility may be found.

4 When the normal rate of destruction has been diminished, the more fragile cells may remain in the circulation for a longer time, and again a wide range of hemolysis may be shown by the hypotonic salt solution test

So far only the red cells have been considered This is a single variable and more easily interpreted, but the observations are so close to the normal that undoubtedly the cells are not abnormal to such an extent that they alone can be used for diagnostic purposes Accordingly, some agent which may with slight changes cause red cell destruction

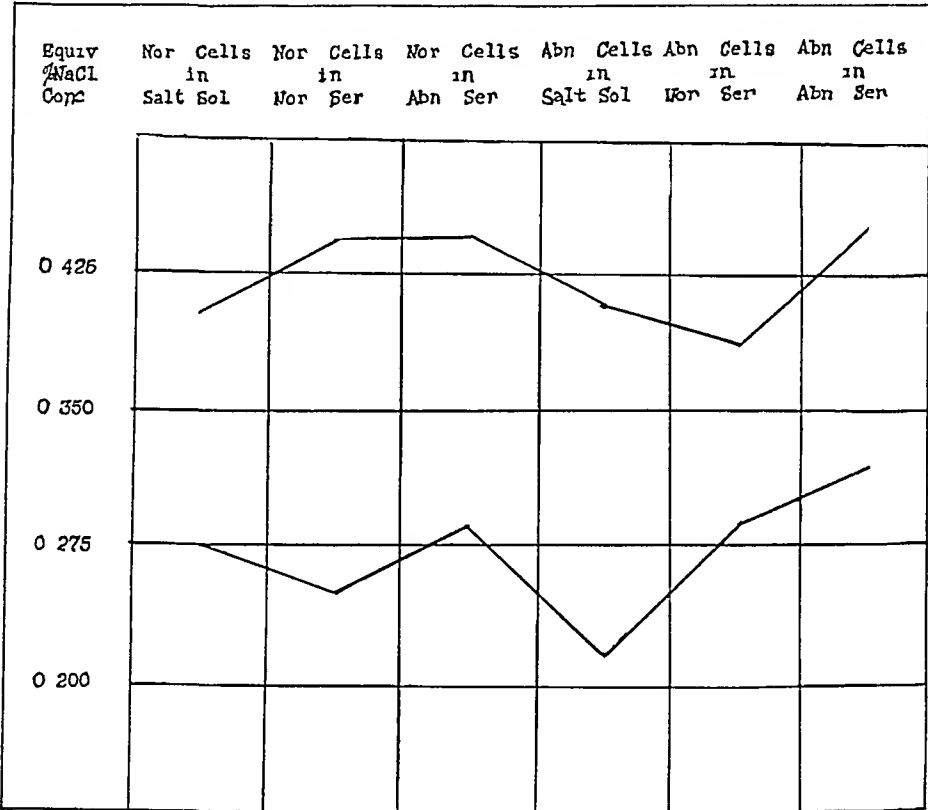


Chart 1—Reaction of reticulated red cells to hypertonic salt solutions and to normal and abnormal serums Reticulated red cells, 43.4 per cent, platelets, 254,000, hemoglobin, 30, red cells, 1,200,000, and white cells, 4,000 In each chart the curves are in pairs, the upper curve the beginning of hemolysis, and the lower curve the completion of hemolysis The space between the two curves represents the range of hemolysis

or preservation was sought The different organs of the body and their extracts were studied as described in the first section of this paper The serum remained uninvestigated

The serum should produce hemolysis and destruction of the red cell at approximately the same level of salt concentration as the hypotonic salt solution, unless some protective or destructive agent was present

In order to investigate this principle, seventy-eight normal cases were tested. The beginning of hemolysis was slightly higher in the serums than in the salt solution. It was the same when the cells were put into their original serum or in that obtained from another person. The serums appeared to be protective for the cells, so that the most resistant cells survived in a lesser salt concentration than in the plain sodium chloride. This seems paradoxical. The range of hemolysis for cells in salt was 0.11, while in serum the average was 0.20. This range must be taken into account when the action of a particular serum on red cells is considered. The variation of any normal from the average of the group of normals is very small, so that any marked deviation from the standard normal can be classed as pathologic (chart 2 A)

Tests in normal cases in all iso-agglutination groups showed

(a) The mean for beginning hemolysis of cells from normal persons in salt solution is 0.40 for seventy-eight cases

(b) Cells from normal person in own serum 0.45

(c) Cells from normal person in serum of another normal person, 0.44

(d) Greatest difference between "a" and "b" is 0.10, and 70 per cent of the cases show a difference of less than 5 per cent

(e) Greatest difference between "a" and "c" is 0.10, and 75 per cent show a difference of less than 5 per cent

(f) Ten of the seventy-eight cases show their own serums less hemolytic than salt solution

(g) One of twenty cases shows other normal serums less hemolytic than salt solution

Average for Hemorrhage—A few hours following an acute hemorrhage from trauma, the cells are normal to salt, but the serum is protective to the cells which it contains and to the cells from another person. Perhaps something other than salt has entered the serum which exerts this action or perhaps the cells have adjusted themselves to the newly formed serum. Since the serum protects both its own cells and those from a normal person, it would seem that the serum itself has changed (chart 2 B)

Secondary Anemia—The average for all degrees of secondary anemia is very nearly the same as normal. In individual cases there are striking variations, as in case 68 of early Hodgkin's disease, the abnormal serum is very protective, while in case 76 that of lead poisoning, the serum is destructive both to normal cells and to its own cells (chart 2 C)

Hemolytic Jaundice—The serum reacts normally with normal cells, but some of the cells are more fragile in normal serum and still more so in their own serum, while there are a rather large number of very resistant cells. The lower curve is the same as that in hemorrhage (chart 2 D)

Pernicious Anemia—Relapse—Septic Anemia—This group included all cases in which the diagnosis could be made by the symptoms and observations of the blood at the time the blood was taken for the test. It was in this group that I noticed the marked hemolytic activity of the serum for normal cells and found it necessary to extend the test to include two series of tubes, one for testing the reaction of abnormal cells to normal serum and the second for abnormal cells to abnormal serum. When normal cells are placed in abnormal

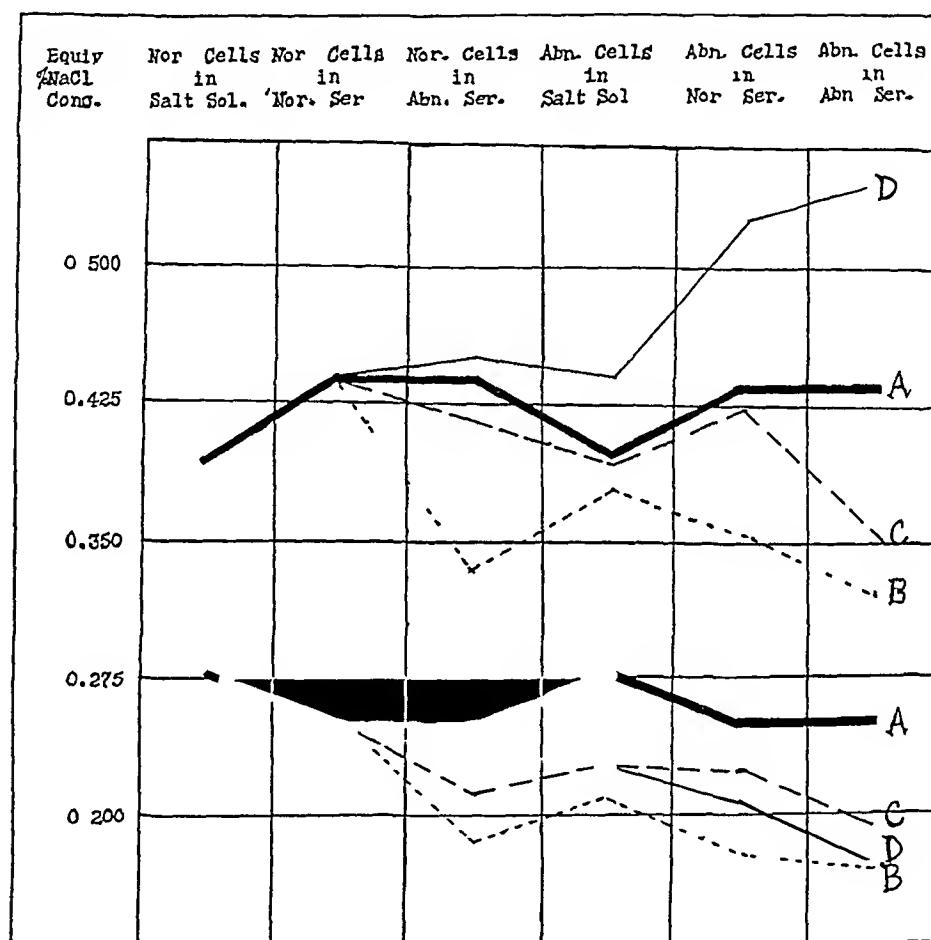


Chart 2—Range of hemolysis for cells in salt solutions and in normal and abnormal serums. A represents the normal average, B, the average for acute hemorrhages, C, the average for secondary anemia, and D, the average for hemolytic jaundice. The lines are in pairs, the upper line indicating the beginning of hemolysis and the lower line the completion of hemolysis.

serum, hemolysis begins at 0.550 (sodium chloride), and when abnormal cells are placed in their own serum, it is increased to 0.58. Many of the cases reach a higher level, as in case 65, to 0.65 and 0.8, case 61, to 0.71 and 0.89. The cells react normally to salt solution. This increased hemolysis in the serum in pernicious anemia is more promi-

ment when the relapse is on the decline and less when on the incline to recovery. In one case it was noticed definitely while the condition was still in remission but just before the relapse which followed in a few days. It would seem from this that some toxic or hemolytic agent is in the serum and that this agent is transitory. If any antibody is formed which causes the remission it is temporary, as a relapse invariably occurs sooner or later. It would be easier to assume that the

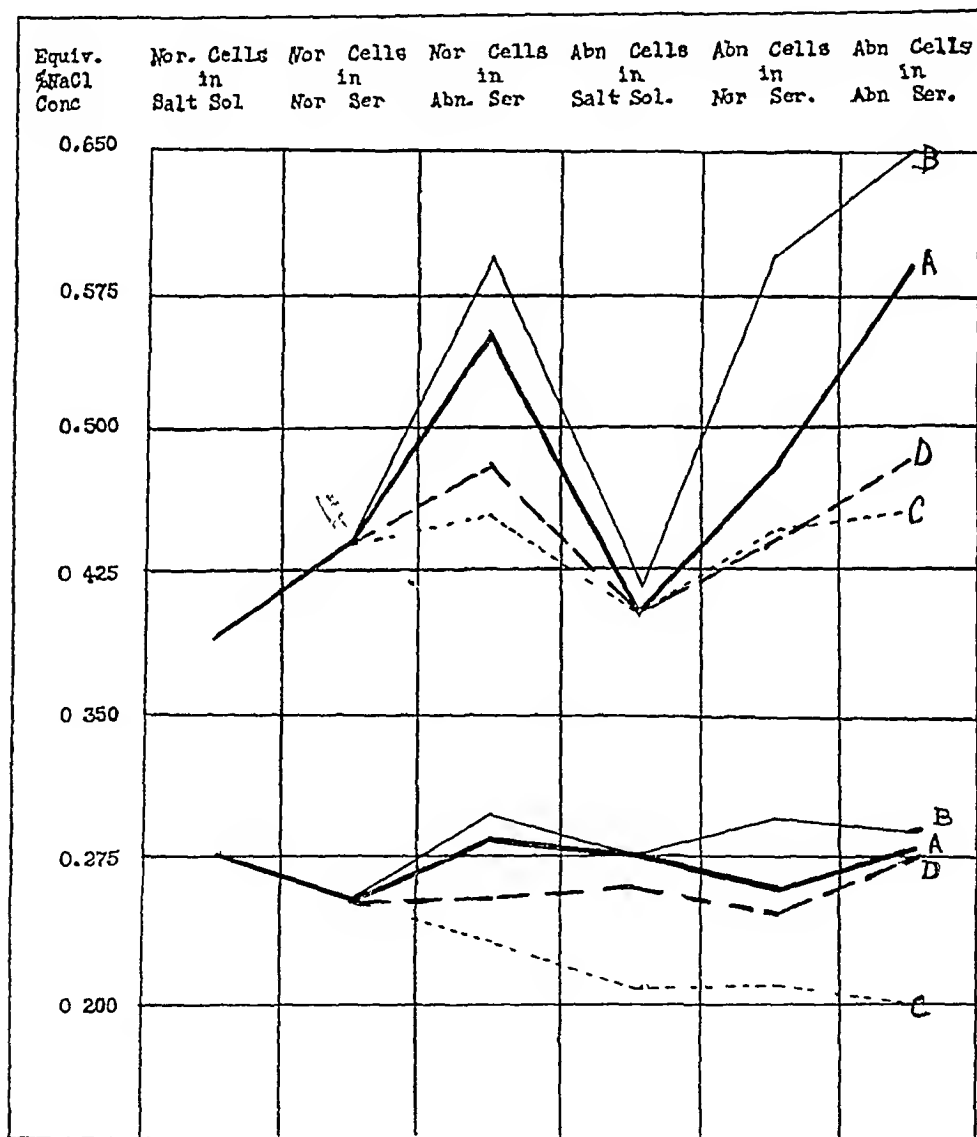


Chart 3—Curves showing average range of hemolysis at the time of blood test. *A* represents the reaction during the period of relapse of a case of pernicious anemia, *B*, the reaction in septic anemia, *C*, the range for jaundice produced by various causes, and *D*, the period of remission in pernicious anemia.

toxic substance appears intermittently in the blood stream. This curve is almost identical with that of septic anemia. In septic anemia there is an absorption of poisons from a definite focus of infection or abscess. Cases of bacteremia were not included in this group (chart 3 *A* and *D*, also chart 4).

Jaundice—This group included the various types of jaundice, except the hemolytic. Two cases were syphilitic. The upper curve is normal. The lower is slightly below the normal. The action of bile in the serum on red cells is slight, either on the normal cells or the cells which were in the jaundiced serum (chart 3 C)

Pernicious Anemia—Remission—The curves are normal. The diagnosis had been made previously when the patients were

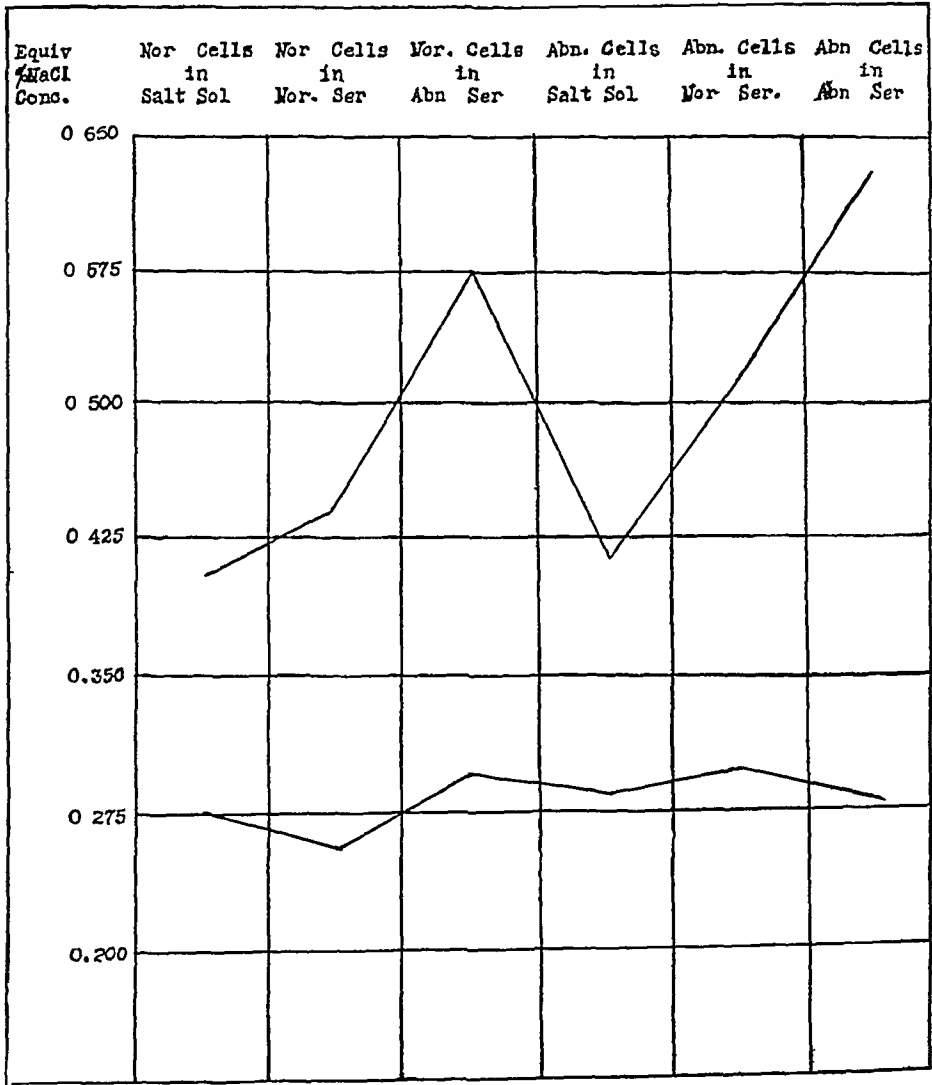


Chart 4—Curves showing range of hemolysis during the period of relapse in a case of pernicious anemia. Hemoglobin, 30, red cells, 880,000, platelets, 112,000 and white blood cells, 4,000

in a state of relapse. There were slight variations of the curve for individual cases, depending on which stage of remission they were in, whether just entering it or ready for a relapse (chart 3 D)

Polycythemia—In polycythemia a portion of the cells were very resistant. Many red cells survived a dilution equivalent to sodium

chloride 0.1, determined by microscopic examination. Some of the cells were slightly more fragile than normal. An interesting question can be raised here as to the cause of polycythemia. The cells may increase in number because they are exceedingly resistant and defy the normal destruction mechanism while the rate of production continues the same.

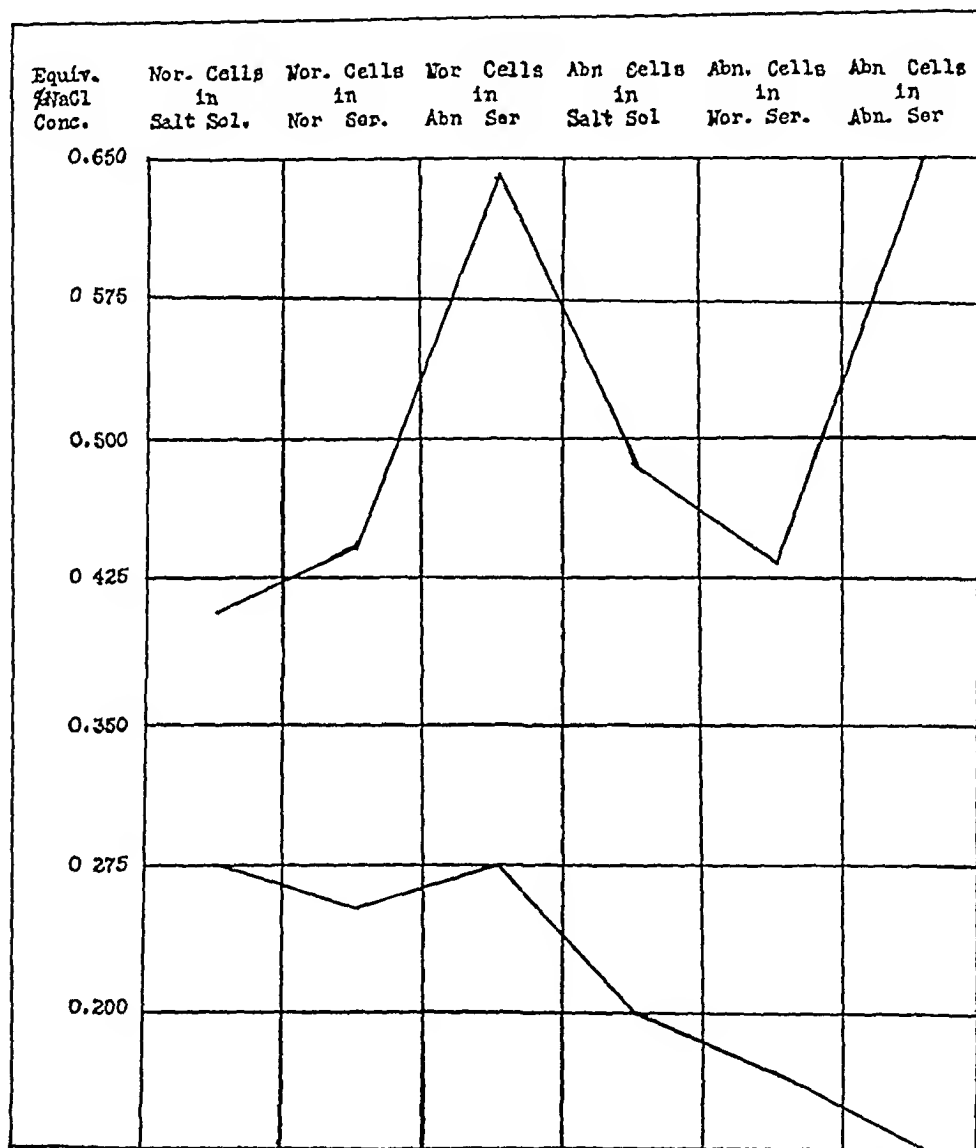


Chart 5—Averages in polycythemia serums, hemoglobin, 140, red cells, 8,620,000, platelets, 260,000, and reticulated red cells, 2 per cent

Unclassified—This includes a variety of cases of known diagnosis and some doubtful

SUMMARY OF CASES

In case 4, the patient had a severe anemia and presented some of the symptoms and signs of pernicious anemia and aplastic anemia, also symptoms of hemolytic jaundice at times. Transfusion was used a

number of times, with temporary relief This test proved that the red cells were at times extremely fragile, being hemolyzed in normal serum with a sodium chloride concentration of 0.89 and her own serum 0.884 The serum was not hemolytic to normal red cells In case 70, one of trichinosis, the blood serum was normal In case 28 which was not diagnosed, the cells were extremely fragile In case 5, hypertrophic cirrhosis of the liver with severe jaundice, the serum was hemolytic In case 40, aplastic anemia, the cells were resistant nevertheless it was necessary to give the patient transfusions every thirty to

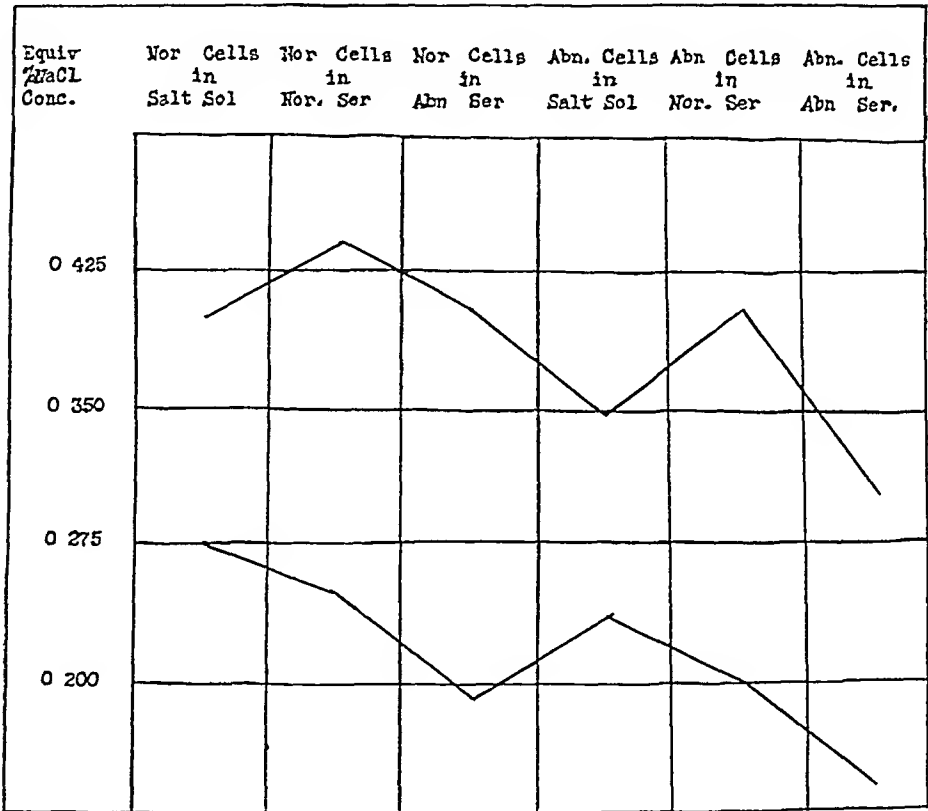


Chart 6—Averages in reaction of cells in aplastic anemia, hemoglobin, 257, red cells, 1,310,000, white cells, 4,200, platelets, 192,000, serum deeply yellow

forty days He felt well in the intervals and did his usual office work (chart 6, also table 2)

CONCLUSIONS

- 1 Under certain conditions there are hemolytic substances in the blood serum The unknown substances act in vitro and may also act in the blood stream on the red cells
- 2 Blood serum in patients with pernicious anemia who are having relapse contains a hemolytic substance for its own red cells and also for normal red cells

TABLE 1—*Characteristic Features of Diseases Studied as Shown by Mean Values in Abnormal Cases*

| Minimal Hemolysis Concentration | Hemorrhage | Aplastic Anemia | Secondary Anemia | Hemolytic Jaundice | Permeious Anemia | Poly- cythemia |
|---------------------------------|------------|-----------------|------------------|--------------------|------------------|-------------------|
| Col 3 | N | — | N | + | N | + |
| Col 4 | — | N | N | + | N | + |
| Col 5 | — | N | — | — | + | + |
| Col 6 | — | — | — | + | + | + |
| Span | | | | | | |
| Col 3 | + | — | N | + | N | + |
| Col 4 | + | — | N | + | N | + |
| Col 5 | N | N | — | — | + | + |
| Col 6 | N | — | — | + | + | + |

Span indicates difference between minimal and complete hemolysis concentration, N, value within normal range, +, value greater than normal maximum, —, value less than normal minimum Col refers to the column in the charts

TABLE 2—*Fractions of Cases Showing Extra Normal Values*

| Minimal Hemolysis Concentration | Hemorrhage | | Aplastic Anemia | | Secondary Anemia | | Hemolytic Jaundice | | Permeious Anemia | | Poly- cythemia | |
|---------------------------------|------------|-----|-----------------|-----|------------------|-------|--------------------|-----|------------------|------|-------------------|-----|
| | + | — | + | — | + | — | + | — | + | — | + | — |
| Col 3 | 0 | 2/6 | 0 | 2/2 | 0 | 0 | 2/2 | 0 | 2/20 | 6/20 | 2/4 | 0 |
| Col 4 | 0 | 5/6 | 0 | 0 | 0 | 3/20 | 2/2 | 0 | 4/20 | 0 | 3/4 | 0 |
| Col 5 | 0 | 5/6 | 0 | 0 | 2/20 | 13/20 | 0 | 2/2 | 17/20 | 0 | 2/4 | 0 |
| Col 6 | 0 | 5/6 | 0 | 2/2 | 0 | 6/20 | 2/2 | 0 | 17/20 | 0 | 4/4 | 0 |
| Span | | | | | | | | | | | | |
| Col 3 | 3/6 | 0 | 0 | 2/2 | 3/20 | 0 | 2/2 | 0 | 2/20 | 5/20 | 3/4 | 0 |
| Col 4 | 4/6 | 0 | 0 | 2/2 | 4/20 | 0 | 2/2 | 0 | 5/20 | 1/20 | 4/4 | 0 |
| Col 5 | 0 | 1/6 | 0 | 0 | 6/20 | 8/20 | 0 | 1/2 | 13/20 | 0 | 2/4 | 2/4 |
| Col 6 | 0 | 1/6 | 0 | 2/2 | 2/20 | 9/20 | 2/2 | 0 | 14/20 | 0 | 4/4 | 0 |

The numerator refers to the number of cases showing extra normal values, the denominator refers to the number of cases of the disease studied

TABLE 3—*Percentage in 110 Cases Studied Showing All of the Deviations from the Normal by Mean Values Including Certain Cases of Slight Deviation from the Normal Obliterated or Only Vaguely Represented in Mean Values*

| Hemorrhagic | Aplastic Anemia | Secondary Anemia | Hemolytic Jaundice | Permeious Anemia | Poly- cythemia |
|-------------|-----------------|------------------|--------------------|------------------|-------------------|
| 50% | 100% | 40% | 50% | 60% | 50% |

TABLE 4—*Percentage of Cases Other Than Disease in Question Showing All Characteristics of Mean Values for that Disease Without Abnormalities*

| Hemorrhage | Aplastic Anemia | Secondary Anemia | Hemolytic Jaundice | Permeious Anemia | Poly- cythemia |
|------------|-----------------|------------------|--------------------|------------------|-------------------|
| 3% | 1% | 2% | 1% | 9% | 0 |

3 Serum in hemolytic jaundice and septic anemia also contains a hemolytic substance

4 The red cells are abnormal in polycythemia, aplastic anemia and secondary anemia

5 Reticulated red cells of normal size are more resistant than the nonreticulated

6 This test is of value in the differential diagnosis of anemia and for determining the resistance of the red cells and the hemolytic power of the serum

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AND

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BALTIMORE

Notation of clinical observations has existed since the beginning of medicine. A large portion of the present knowledge of disease has come from the summation of the bedside notes made by the physician. Before the occurrence of comparatively recent scientific trends in modern laboratory medicine, the clinical record might well have been considered as the corner-stone on which all medical knowledge was built.

In the past three decades the basic medical sciences have advanced with tremendous strides. The microscope and the test tube have yielded scientific facts of utmost importance. The knowledge obtained from observation made at the bedside has progressed with the advance in laboratory medicine but has scarcely kept pace with it. This is due, in part at least, to the ignorance displayed by the clinical group in modern statistical technique. The analysis of clinical records, which is the scientific proving ground for clinical observation, has been carried on in an inadequate fashion. The reason for the failure to use the statistical science may be assigned largely to the form of the clinical record which does not yield itself to technical analysis. Modern tabulating techniques are available which, if applied to the problem, should fulfil the demands of statistical medicine, permit extensive analysis of clinical facts and consequently furnish a yardstick for clinical procedures.

Only one essential difference exists between the demands of statistical medicine and those of clinical medicine. Statistical technique demands completeness of negative as well as of positive information for all items of sufficient importance to be considered a part of the disease syndrome. In clinical medicine completeness is interpreted in terms of positive facts about the case, but notation of the bulk of negative observations is ignored. The laws of probability cannot be applied unless the true

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* The death of Dr. Reed Rockwood occurred after this article was accepted for publication. The loss of his scientific interest and zealous cooperation in laboratory and clinical research problems is keenly felt by his co-workers.

probabilities are known. If all the negative observations are not present, these true probabilities cannot be calculated.

In the writing of the history and physical examination as it is carried on at the present time, practical difficulties arise to prevent the satisfactory notation of negative observations. The physician cannot and will not take the time to write a list of negative answers, consequently it is almost hopeless to expect complete notation in the history and physical examination as it is done today.

On the other hand many valuable features of the clinical chart in its present form must not be sacrificed for the completeness so desirable in any numerical analysis. The ideal record for both clinical and statistical medicine must be individualistic and personal in character. Questions in the history must be asked in the proper sequence. The notation of negative data should be so facilitated that it does not add a burden to the duties of the physician. The record should be sufficiently elastic to meet all demands put on it, and it should yield information readily. A single glance at the clinical record should suffice for the consultant to locate the particular item in which he is interested while he is standing by the bedside of his patient.

During the last year we have developed a chart for general history and physical examination (fig 1) which seems to fill the needs of both clinical and statistical medicine. The chart has been filled out for the hypothetical diabetic record of Mrs H Brown, and this case will be used for illustrative purposes throughout the paper. The chart has been devised with a view of conserving the physician's time and effort and at the same time of obtaining a far more complete set of clinical data concerning the general case. It has had the advantage of rather widespread general criticism and of detailed scrutiny from a number of physicians. When possible, every feasible suggestion was worked into the chart.

We do not expect that this record will prove satisfactory in all types of institutions. In all probability, it will be too extensive for physicians to use in their private practice or for dispensary services. We are at present working on an abridgment suitable for both the private physician and the dispensary. The present chart was devised for the record of the patient in a hospital on the average hospital service. The questions and notations represent our idea of a minimal requirement for a reasonably complete routine clinical record in a hospital.

The form does not represent a complete system of records. There are many medical specialties such as eye, ear, nose and throat, dentistry, obstetrics, psychiatry, neurology, dermatology and others which are inadequately represented by this chart. The general history and physical

examination is intended to be the hub in a wheel of medical records. The records of specialties will dovetail into this general chart without overlapping, consequently, the items in the chart are always in the form of leading questions and leading physical observations which, if positive, will suggest a special, more detailed examination.

It is important to note that the use of this chart does not curtail any type of history or physical examination in use at present. There is sufficient writing space to expand the data whenever it is desirable. In case insufficient blank space is allotted in the booklet, blank sheets may be inserted at any place, in fact it is considered highly desirable to expand the routine questions and notations. Good records can be obtained only by amplification of positive answers and observations.

The entire first sheet of the history is occupied with routine facts customarily demanded in all histories. If a specific institution has its own diagnosis sheet, it is not necessary to use the few lines allotted on this chart for that purpose, otherwise the diagnoses are listed in this space.

The present illness is to be noted in chronologic order. The routine questions of the past and present illness (fig 1, pp 4 and 5) have been printed in the words which a physician uses in talking to his patient. Whenever possible the necessity for definition of medical terms was avoided, since the phrasing of questions differently by various physicians would undoubtedly elicit a variety of answers from the patient.

There are only three ways in which a given question can be checked. The check mark means positive, the zero means negative and a question mark signifies unknown. If a question is left blank, it is considered to be unasked. Unasked questions defeat the purpose of the chart, which is to gain completeness. In certain places, the brackets list subquestions which do not have to be asked, for example, under the respiratory system (fig 1, p 4), if the patient said he did not have tonsillitis or sore throat, it would be unnecessary to ask about the frequency of attacks. If the answers to the questions in an entire section should be negative, one zero written on the main section heading would indicate that the questions under all subheadings had been asked and the answers found to be negative. For example, the genito-urinary system (fig 1, p 5) is indicated in this manner. If the answers for any column of questions are negative, a zero can be written after the first and last question, and a straight line drawn between the zeros to show that those for all intervening items are likewise negative. For example, under respiratory system (fig 1, p 4) all answers between nosebleed and night sweats inclusive are indicated to be answered in the negative in this manner. By means of these short cuts negative notations are reduced to a minimum.

After each system, in both the history and physical examination, the physician is requested to interpret the symptoms of the entire section in view of what significance these symptoms mean to him at the moment. For instance, a number of observations on the heart were checked (fig 1, p 11), and the summary reads "Heart moderately enlarged, functional murmur"

The routine facts of the history are placed on page 6. The notation of the family, marital and menstrual history and of habits is self-explanatory. Degrees 1, 2 and 3 signify mild, moderate and excessive, respectively. Definition of the limitations of these degrees will not be attempted. They are qualitative measures and will be used as such. The specific institution or physician using the chart may define degree as desired.

The last section in the history represents somewhat of an innovation. It is well recognized that histories are not of the same quality or statistical value, consequently, the physician is requested to grade the history after he has finished writing it. For example, in the record of Mrs. H. Brown, this section is marked zero, which indicates a satisfactory history.

The first page in the section on physical examination calls for the routine measurement of height and weight which is customary in most medical services at the present time. If the patient is too sick to obtain his weight on admittance, this measure may be filled in at a later date and the date noted in parenthesis. Surface area is a computed constant and does not need to be recorded unless it is desired by the specific institution.

If the notation of an intern is checked by a consultant, it is possible for the latter to recheck the same chart with a different colored writing fluid. When differences between the notes of the consultant and intern exist, the notes of the consultant should be accepted by the record department.

Several lines are allowed for the general description of the patient. A considerable group of internists consider that such a statement is more important than any other item in the physical examination. A terse description is requested which will be sufficiently accurate so that a visiting physician can select the patient among many others. It forces the examiner to observe the patient as an individual.

Two pages are left for description of the principal abnormalities in the words of the examiner. It would be ridiculous to assume, for example, that the checking of the routine observations on the heart would give a good picture of a disturbance of the heart. A graphic detailed description of such an abnormality is indispensable. In the

illustrated diabetic case of Mrs H Brown, it was not necessary to describe in detail any of the summarized principal abnormalities (fig 1, p 7)

Before writing the results of the routine physical observations the physician will examine his patient from head to foot in the customary manner. He will then sit down to check the chart. All of the items listed are abnormalities, consequently, even if the physician does not have certain specific points in mind when he examines the patient, he recognizes the absence of such abnormalities. He is able to scan the list, and frequently to answer entire sections without referring to the patient. In case he overlooks the observation of a few items, it is reasonable to expect him to recheck these points.

As in the history, zero indicates a negative answer, a check mark a positive one, and a question mark, doubtful observations, there should not be any blanks or unanswered items. Degrees are noted as 1, 2 and 3, indicating mild, moderate and excessive, respectively.

The location of abnormalities in the spine, lungs, heart, abdomen, extremities and skin is required. The location of symptoms of the spine and skin is accomplished by a cross line drawn from the symptoms to the involved parts. In the case of disease of the lungs, heart, abdomen and extremities, the location of symptoms is obtained by a line drawn from the symptoms to the diagram. For example, the location of râles (fig 1, p 10) is noted on the diagram by a line from both bases posteriorly to the type of râles found in this location.

The clinical value of mensuration of the heart is a debatable question. It was only after considerable discussion with heart specialists that a decision was made to require a measurement of the right and left border of cardiac dulness at the level of the second rib and apex. These measurements can be made in centimeters by the scale printed on the edge of the sheet. A sketch of the outline of the heart is desirable but cannot be expected as a routine notation. Accentuation and diminution of the heart sounds and heart murmurs must be located in respect to the aortic, pulmonic, mitral or tricuspid areas.

Under neurologic observations, the degrees 1, 2 and 3 have been extended to the negative side of normal, and signify diminished, moderately diminished and absent reflexes, respectively.

The term "sensitive achilles' tendon" needs explanation. Libman has shown that by deep, steady pressure over the styloid processes and by noting the response of the patient, he has a rough measure of the reaction of the patient to unpleasant sensations. This reaction forms an excellent guide to the evaluation of the symptoms concerning which the patient complains. The response can be controlled by pressure over the mastoid bone which is not normally unpleasant.

Present Illness (Chronological Order)

Loss of Weight Amount 30 lbs, Duration 1 yr.

Loss of Strength Degree 1, 2, 3, Cot, Duration 1 yrs.

1st Date When Patient Was Well Fall, 1926 Date Onset of Symptoms Aug. 1927

Ditto Patient was last perfectly well about a year ago At this time she

1926- began to notice a little loss in weight altho her appetite was still

rather good. She began to notice that she could not do her housework

as well as formerly and would seem to tire more easily. This sensation

of weakness gradually became progressively worse She also noted that

she could be dizzy on sudden change of posit on of the head, such as

on getting up suddenly or out of a chair or on getting up in the morning

Aug. During this month she noted a headache on rising nearly every morning

1927. fronto-occipital in type, which wore away during the course of the day.

This run relieved to some extent by taking salicylic acid

Date

[illegible]

Fig 1—Form for recording general history and results of physical examination. This form is used as a twelve page (six left) booklet, 8½ by 11 inches in size. It is filled out with the illustrative case record of Mrs H H Brown.

No 67,190 PHYSICAL EXAMINATION Date Sept. 1, 1927

Patient's Name Mrs. Harold Brown Examiner Harris Consultant, Rochester
(see different entry 1 & 2 per vol)

Height (in or cm) 5'4" Weight (lbs) 160 Surface Area (sq m) _____

Temp (Mouth, Rectal) 98.4
(15 min 1-11)

General Description of Patient

Somewhat obese, elderly, gray-haired woman lying in bed.
Seems a little dull mentally.

Detailed Summary of Principal Abnormalities

1. Nephritis
2. Dehydration
3. Non-toxic adenoma
4. Pilon at base
5. Cardiac hypertrophy
6. Hypertension
7. Hemorrhoids
8. Peripheral arteriosclerosis
9. Toxemia
10. Obesity

LABORATORY AND SPECIAL EXAMINATIONS

[illegible]

Page 1

Fig. 2—Loose-leaf laboratory sheet printed on both sides. It is filled out with laboratory observations made on Mrs. H. Brown

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Patients may show varying grades of hypersensitiveness and hyposensitiveness. One of us has tried this test and believes that it is important, but that for the average patient it is better elicited by firmly squeezing the achilles' tendon. The amount of reaction on the part of the patient is then noted on the chart by the numbers 1, 2 and 3 on the positive or negative side of normal.

No. 67,190 Name Mrs. Harold Brown

Date _____

Dining
Hall

Fig 3—Loose-leaf supplementary blank sheet, printed on both sides

The primary impression represents a summary of the observations, both history and physical, after the first examination of the patient has been completed

It will be noted that the chart has been copyrighted in the names of Dunn and Rockwood this was done solely to protect it from com-

mercialization, and permission will be granted freely for any physician or medical institution to reprint it for professional purposes

The laboratory sheet (fig 2) is original in construction but not in content. It does not demand special description. It was formulated primarily with the intention of incorporating the cross-index feature, to be discussed later, into laboratory observations.

The blank sheet (fig 3) can be used to fill in for additional space at any part of the record.

The physical form of the chart has been planned with the following specifications:

- 1 The general history and physical examination are bound and printed together in the form of a twelve page booklet. This booklet can be printed with binding margin at either the side or the end of the chart as desired. The order of the sheets is the same whether the pages turn as in a book, or whether they are bound so as to open lengthwise.

- 2 The laboratory and blank sheets are printed on both sides as detached papers.

- 3 The entire form will be on letter-size paper, 8½ by 11 inches which is the size suitable for the standard files of all hospitals.

- 4 In order to obtain the maximum efficiency in the mechanical handling of these charts, it is essential to have a unit number for each patient, and it is desirable to keep all records of the patient in a unit file rather than in a bound volume.

- 5 The lines throughout the chart are so spaced that double or triple space on all standard makes of typewriters will allow the type and printed lines to coincide.

- 6 The cheapest quality of paper which can be used is a 24 pound basic ledger substance. This paper is not regarded by paper manufacturers as permanent since it has a low percentage of rag in its composition. It is a better grade, however, than most of the paper used in the majority of hospitals at the present time. To demand a more permanent paper would raise the entire question of the length of time which hospital records should be kept—a discussion beyond the scope of this publication.

- 7 The testing of this chart is now in progress at six hospitals. It is also being tried out by a number of physicians in their private practice. In this trial the chart will be subjected to actual working conditions. If it is possible to obtain completeness in the notation of all the required facts in the majority of cases without interference or handicap to the clinical routine, the chart will be considered successful. There are many questions which must be answered before the material in these records can be analyzed with a maximum degree of efficiency.

The variation between observations of physicians with different degrees of medical experience, the variation in answers due to questions being purely subjective or objective in character, the variation in a given patient in his reaction to different physicians, in his answers under various diseases or mental conditions, and the variation of the patient on successive examinations, these and kindred questions must be answered before the reliability of the facts in the chart can be determined

The points in favor of this form for recording the results of general history and physical examination may be summarized as follows

- 1 It is just as individualistic as the types used by physicians at the present time for recording the history and the results of physical examinations. It sacrifices none of the sequence in disease events and none of the personal elements existing between the patient and the physician

- 2 The chart definitely facilitates the notation of clinical facts

- 3 It yields information much more readily than the present forms in common use because a given fact is located in a specified section

- 4 The accuracy of the record depends entirely on the competency of the physician. The element of forgetfulness on the part of the examiner is practically obviated

- 5 The chart will be more legible than if it were entirely in handwriting

- 6 The record of the case is sufficiently elastic to meet most demands in modern medicine. In case a given institution has a great many patients of a certain type it may be necessary to amplify this general form with a special printed sheet, giving the specific questions and observations desired, as, for example, one suitable for the record of a patient with diabetes, cardiac or dermatologic conditions

- 7 The record will be far more complete in respect to negative information than any existing type

- 8 It should prove to be a considerable aid in the training of students. It will facilitate the orderly arrangement of their clinical ideas, and will point the way to the art of history taking, which involves the following up of leading questions and observations

- 9 It will afford an opportunity for one to measure the variability in recorded facts due to the personal equation of the examiner or of the patient

- 10 It will furnish adequate statistical material for the clinician interested in the analysis of disease entities

- 11 With all of these advantages, the time of recording the history and physical observations is reduced, as compared with present records of equivalent value

12 The adoption of a record form of this general type is essential if the physicians in a hospital hope to obtain an adequate cross-index of the contents of their records

The technical features of the cross-index will now be considered in detail

DESCRIPTION OF MECHANICAL CROSS-INDEX

A mechanical cross-index scheme has been worked out for the clinical record just described. It may or may not be used, as desired. An attempt will not be made in this article to describe the numerous systems of cross-index which are in use at the present time in hospitals throughout the country. After a careful consideration of modern methods of tabulation, the mechanical punch-card system was selected as the best available tool to bring about a solution to the problems in the cross-indexing of hospital records.

Raymond Pearl first suggested the adaptation of a mechanical punch-card as a medical index method. A detailed description of his plan is given in the original article¹

Although the system proposed by Pearl has an enormous advantage over any other developed in the past, owing to its elasticity and the mechanical handling of information, certain difficulties arise in the practical application of his plan

1 The use of multiple secondary cards complicates the index

2 Multiple entries in the history and physical observations are frequently a desirable feature in the search for records

3 The entire index is kept up in the form of a number of punch-cards in each case. As records pile up in numbers, mechanical sorting, rapid as it is, will become a considerable chore when tens or hundreds of thousands of cards are manipulated. Moreover, punch-cards kept too long a time will wear out, become swollen from dampness and will jam in the machine

4 The adaptation of the index plan depends on the rental of tabulating machinery by all hospitals, the expense of which most small hospitals would find prohibitive

Before describing the index system which we propose in connection with this record, it is desirable to list the needs which should be fulfilled by an ideal cross-index for hospitals. The essential features are as follows

1 The index should show the location of the record of any case desired by the physician within as brief a time as possible

2 It should prevent the misplacement of records owing to multiple or ambiguous diagnoses

1 Pearl, Raymond. Modern Methods in Handling Hospital Statistics, *Bull Johns Hopkins Hosp* 32 184, 1921

3 It should permit the location of records by the history, physical and laboratory observations, as well as by diagnoses

4 It should fill the needs of a small hospital with about the same efficiency that it does a larger one

5 It should be adequate for departments of hospitals engaged in specialized branches of medicine

6 It should be simple technically, in order to be kept by ordinary clerical help

7 It must be economical

Without checking over the good or bad points of any particular system, it would be generally admitted by physicians who have analyzed clinical records that, at the present time, the existing methods of cross-index do not measure up to all the features in the ideal system just enumerated

A description of the cross-index used in this chart may be divided into seven parts

1 Description of a punch-card for general purposes

2 Description of the specially printed punch-card used in the proposed index

3 Description of the codes used in the index which are as follows: code for diagnosis, for age, for sex and color, for outcome of case and civil state, for history, for height, for weight, for physical examination, for laboratory observations, and for miscellaneous items of interest

4 Description of the technic of punching cards and what it means to the record department of the average hospital

5 Description of the printed cross-index

6 Estimation of the cost of a mechanical index system

7 Summary of arguments for the mechanical cross-index

DESCRIPTION OF A PUNCH-CARD FOR GENERAL PURPOSES

A punch-card for general purposes is shown in figure 4. This card is $7\frac{3}{8}$ by $3\frac{1}{4}$ inches in size. It is printed by both the Powers Accounting Machine Corporation and the International Time Recording Company, which are the two principal competitors in this field. Holes have been punched in this card by a machine which will be described later. There are forty-five columns of numbers on the card. Each column runs from zero to nine in value. The small numbers at the bottom of the card represent the number of the column and are never punched. Any one of the numbers from zero to nine can be punched in any one of the forty-five columns.

Ordinarily, only one number is punched in a given column. Although there are only ten numbers printed in any given column, there are twelve possible positions that may be punched. The eleventh position (also called the X position) has been punched in column 15. The twelfth position (also called the blank position) has been punched in

number which can be recorded is 999999 and allows, therefore, for a tabulation of that many separate patients

Columns from 7 to 21 are set aside for diagnoses Three columns, 7, 8 and 9, are allotted for the first diagnosis and two columns each are allowed for the remaining diagnoses The first column in each diagnostic field, namely, 7, 10, 12, 14, 16, 18, and 20 can be double-punched² In each of these first columns the blank position represents 1, the X position 2, and the zero position 3 in units of 10 It is possible by this means to indicate forty numbers in one column The number zero will be indicated if a hole is not punched in the column, and numbers from 1 to 9 if the printed numbers from 1 to 9 are punched If the blank position is punched, it will signify code no 10 The numbers from 11 to 19 will be indicated by a double punch, namely, the blank position for the 1 in units of 10 and the proper unit number

| Case. No. | Diagnoses | | | | | | | Age | Sex | Marital | Occupation | History | Physical | Exam. | Lab. | File |
|--------------|-----------|-------|-------|-------|-------|-------|-------|-------|-------|---------|------------|---------|----------|-------|-------|-------|
| | #1 | #2 | #3 | #4 | #5 | #6 | #7 | | | | | | | | | |
| 0 0 0 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 | 0 0 0 |
| 1 1 1 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 | 1 1 1 |
| 2 2 2 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 | 2 2 2 |
| 3 3 3 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 | 3 3 3 |
| 4 4 4 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 | 4 4 4 |
| 5 5 5 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 | 5 5 5 |
| 6 6 6 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 | 6 6 6 |
| 7 7 7 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 | 7 7 7 |
| 8 8 8 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 | 8 8 8 |
| 9 9 9 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 | 9 9 9 |
| 1 2 3 4 5 6 | 7 8 9 | 10 11 | 12 13 | 14 15 | 16 17 | 18 19 | 20 21 | 22 23 | 24 25 | 26 27 | 28 29 | 30 31 | 32 33 | 34 35 | 36 37 | 38 39 |

Fig 5—Punch card printed as an index card for the general medical examination

from 1 to 9, no 20 by a single punch in the X position which represents 2 in units of 10, nos 21 to 29 by a double punch, one of which is the X position representing 2 in units of 10 and the other the proper unit number from 1 to 9, no 30 by a single punch in the zero position which stands for 3 in units of 10 and numbers from 31 to 39 by a double punch, one of which is the zero position representing 3 in units of 10 and the other the proper unit number from 1 to 9

The second column in each diagnostic field is punched in one position only Eleven positions may be indicated in this column which are, respectively, the blank position, 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9 It is possible, therefore, to code into hundreds in each two-column field for any given diagnosis The numbers would read serially as 00-blank,

² In order to accord with the wiring possibilities of the printing tabulator only twenty-five columns can be double-punched We have taken advantage of every one of these possibilities in the proposed cross-index card

000, 001, 002, 003, 004, 005, 006, 007, 008, 009, 01-blank, 010, 011, 012 etc., up to the highest number which would be 399. Counting the blanks and zeros as separate numbers, this code permits the division of each diagnostic field into forty major headings in the first column with a subdivision of each of these into eleven subsidiary units in the second column. The total number of items which it is possible to list in the two-column field by this process is 440.

A survey made in several hospitals shows that usually in about 80 per cent of the case records there is only one diagnosis. Multiple diagnoses up to four are fairly common, and over seven extremely unusual. The first diagnosis, columns 7, 8 and 9 has a third column, no 9, which permits the subdivision of each of the 440 items in the first two columns into eleven subsidiary units allowing for 4,840 items in the code of the first primary diagnosis.

| Case No. | Diagnoses | | | | | | | Age | Sex & Col. | Contact | History | | | | Physical Exam. | | | | | | | | | | | Lab. | Vis. | Index |
|----------|-----------|----|----|----|----|----|----|-----|------------|---------|-----------------|-----------------|--------------|--------|----------------|-------|------------|----|---------|-------|-----|-------|------|------|------|-------|-------|-------|
| | #1 | #2 | #3 | #4 | #5 | #6 | #7 | | | | Chief Complaint | Present Illness | Past Illness | Weight | HT & WT | Temp. | Pulse & R. | BP | Respir. | Card. | Ab. | Stom. | Gen. | Neu. | End. | Spec. | Spec. | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 1 | 2 | 1 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 |

Fig 6—An index card for the general medical examination, which has been punched for the illustrative diabetic record of Mrs H Brown, noted in figures 1 and 2

If there should be multiple diagnoses of eight or more numbers for any given hospital record, the code number of these diagnoses should be written in ink on the back of the card. Any card which has been punched for seven diagnoses must be examined for written code numbers on the back. It is estimated that this event should not occur more than once in two or three hundred times.

In the record of Mrs H Brown, illustrated in figure 1 there are seven diagnoses. These diagnoses with their respective code numbers are as follows: (1) diabetes-mellitus (6 blank), (2) obesity (60), (3) diabetic acidosis (63), (4) general arteriosclerosis (80), (5) hypertension (81), (6) chronic constipation (124) and (7) hemorrhoids (126).

The diagnostic code has not been filled out to thousands and, consequently, the third column in the first diagnosis is left unpunched. The code number of diagnosis 1 (6 blank) is punched in columns 7 and 8, that of diagnosis 2 (60) in columns 10 and 11, of 3 (63) in columns 12 and 13, of 4 (80) in columns 14 and 15, of 5 (81) in columns 16 and 17, of 6 (124) in columns 18 and 19, and of 7 (126) in columns 20 and 21.

The next four columns of the punch-card from 22 to 25 represent the items of age, sex, color, outcome and civil state. Age is coded in columns 22 and 23, sex (male or female) and color (white or black) in column 24, outcome (well, improved, same, worse or dead) and civil state (single, married, widowed, divorced or separated) in column 25. For example, the age of Mrs. H. Brown (fig. 6) is indicated as 49 in columns 22 and 23, the sex (female) and color (white) are coded as no. 2 in column 24, and civil state married and outcome improved by code no. 7 in column 25.

The main divisions of the history occupy four columns from 26 to 29, each is double-punched, using the blank key as 1, the X key as 2 and the zero key as 3 in units of ten. By this means, numbers up to forty can be indicated in the same manner as described for the first column of each diagnostic field. Column 26 represents past illnesses including abnormalities in the weight curve (fig. 1, p. 6), 27, the respiratory, circulatory and gastro-intestinal systems, 28, the genitourinary and nervous system, and column 29, the routine history and the clinician's opinion of the accuracy of the history.

Only thirty-one numbers of the possible forty are used in each one of these columns. Each of the thirty-one numbers represents an abnormality or combination of abnormalities. It is possible to list five separate items or any combination of these five items by use of the combination code printed on the history (fig. 1, p. 4). The past illness, for instance, is divided into five subdivisions. If any one of the diseases from typhoid to scarlet fever has been checked in the past illness, no. 1 is marked as positive. If the patient has had syphilis, gonorrhea or a history of abnormal weight curve (p. 6),³ no. 2 is checked, if he has had a major operation or accident, no. 3, a nose or throat operation, no. 4, and if there is some important item in the miscellaneous, not included in the routine list of past illnesses, no. 5 is checked.

3 The code position of the weight curve is placed with past illnesses, while its chart position naturally falls after the routine question by systems. It represents the only divergence in the arrangement by order between the index code and the printed chart.

If the patient has only one of these five conditions, for instance no 2, the coded number would be identical to the number checked on the chart. If, however, he had items 1, 2 and 4 checked, this combination would be indicated by code no 17 in column 26 of the index card.

In figure 1 code no 26 is punched in column 26 representing positive observations in the past illness in items 1, 2, 3 and 4. Likewise, code no 17 in column 27 represents positive observations in items 1, 2 and 4.

Body height, grouped by classes, is given in column 30, and body weight, also by classes, in column 31. Mrs H. Brown has a stature of 64 inches (162.56 cm) represented by code no 7 in column 30, and a body weight of 160 pounds (74.4 kg) indicated by code no 7 in column 31.

The physical examination occupies eight columns, from 32 to 39, each one of which is double-punched, so that it can represent numbers up to 40. All of the code numbers in the physical examination stand for abnormalities. In column 32, abnormalities of the head and face are noted, 33, of the mouth and throat, in 34, of the neck, spine and thorax, in 35, of the chest and lungs, in 36, of the heart, in 37, of the vessels and abdomen, in 38, of the extremities and neurologic symptoms and 39, of the lymph nodes, skin, genitalia, rectum and abnormal psyche.

Abnormal laboratory observations are indicated in columns 40 to 43.

Columns 44 and 45 have been set aside for miscellaneous conditions and may be assigned in any way desired by a specific institution. We suggest a certain arrangement which may or may not be followed. In this arrangement, four conditions are coded in column 44 which might exist in any diagnosis or any case, namely, autopsy, major operations, minor operations and previous admissions. This leaves a fifth blank space for some special interest still unassigned. Column 45 could be reserved for the indication of the principal service on which the patient was treated. Many hospitals would not desire to make such a distinction between their records.

DESCRIPTION OF CODES USED IN THE INDEX

Code for Diagnosis—Various codes for diagnoses, particularly the international code of death and the morbidity code used by the United States Navy, were scrutinized with a view to molding them into a code for diagnosis to be used in hospitals. We found all of these codes undesirable for general use in a hospital, the principal objection to them is that they have been formulated in a fixed, inelastic manner. The purpose of the diagnostic code for hospital use is to facilitate the location of records. The coding of diagnoses to a degree of minutiae that involves the recording of isolated individual cases will defeat the essential purpose of the code, namely, speed in the search for required

records. The code must be elastic if it is to fill the needs of various types of institutions. For example, a hospital for the treatment of patients with a disease of the eye will need a complete code for observations on the eye, and nothing but the major headings in most of the other groups. The tuberculosis sanatorium will need detailed questions on the diagnosis of the chest and the obstetric department a special amplification on obstetric complications.

The code for diagnosis represents a skeleton outline on which any institution may build its respective diagnostic interests. Each item which has been entered in the outline, both major headings and subdivisions, has been selected after a survey of numerous hospital reports, and entered in the code only if a widespread occurrence of that particular diagnosis exists and if it represents a significant proportion of the total number of patients treated in a hospital.

It is to be noted that there are six major divisions in this code which have been left unassigned so that any institution may indicate as a major interest some unusual local activity. Likewise, there are two or three unassigned subdivisions under each major division. It is important to note, also, that the last major heading is reserved as a miscellaneous group for those diagnoses which do not fit in any of the other groups. The last subdivision under each one of the major headings is reserved as a miscellaneous section. A good rule to follow in the development of a practical code for diagnosis is always to keep the miscellaneous groups below 5 per cent of the total number in its particular section. If some element causes the miscellaneous column to mount above this 5 per cent limit, it should be separated from the miscellaneous group and placed in the code as a separate element.

The code for diagnosis, therefore, is only an outline around which a particular selection of items should be arranged which will best suit the needs of the institution using the code.

Code for Diagnosis

0 blank to 29 Communicable diseases (except 3 blank to 49)

- 0 (blank) Diphtheria
- 00 Dysentery (including all forms of amebiasis)
- 01 Erysipelas
- 02 Fevers of unknown origin
- 03 Gonococcus infections
- 04 Influenza
- 05 Malaria
- 06 Measles
- 07 Mumps
- 08 Mucoses (diseases caused by fungi)
- 09 Parasites and parasitic insects (diseases due to including scales, pediculosis chiggers and others)

- 10 Protozoa (diseases due to, with the exception of malaria, amebiasis and syphilis)
- 11 Pertussis
- 12 Pneumococcus infections and other pneumonias
- 13 Rheumatic fever
- 14 Septicemia
- 15 Typhoid fever
- 16 Diseases of the upper respiratory tract
- 17 Varicella
- 18 Variola
- 19 Vincent's angina
- 20-28 Blank
- 29 Miscellaneous

3 blank to 39 *Syphilis*

- 3 (blank) Diagnosis by serology and otherwise not clinical
- 30 Early infections
- 31 Late infections of central nervous system
- 32 Late infections of vascular system
- 33 Late infections of skin and mucous membranes
- 34 Late infections, visceral
- 35 Congenital infections
- 36-38 Blank
- 39 Miscellaneous

4 blank to 49 *Tuberculosis*

- 4 (blank) Pulmonary
- 40 Bone and joints
- 41 Lymphatic system
- 42 Gastro-intestinal tract and peritoneum
- 43 Genito-urinary system, both male and female
- 44 Skin and mucous membranes
- 45-48 Blank
- 49 Miscellaneous

5 blank to 59 *Ncoplasms*

- 5 (blank) Benign growths
- 50 Carcinomas of gastro-intestinal tract
- 51 Carcinomas of female reproductive organs (including breast)
- 52 Carcinomas of skin and mucous membranes
- 53 Miscellaneous carcinomas
- 54 Sarcomas
- 55 Other types of malignant tumors
- 56 Tumors the type or malignancy of which is in question
- 57-58 Blank
- 59 Miscellaneous

6 blank to 69 *Metabolic and deficiency diseases*

- 6 (blank) Diabetes mellitus
- 60 Obesity
- 61 Undernutrition (including starvation)
- 62 Dietary deficiencies (including rickets)
- 63 Acidosis and alkalosis
- 64-68 Blank
- 69 Miscellaneous

- 7 blank to 79 *Diseases of blood and blood forming organs (except 3 blank to 59)*
- 7 (blank) Anemia (including primary, secondary, hemorrhage and others)
 - 70 Leukemias and Hodgkins
 - 71 Purpura and hemorrhagic diseases of the new-born
 - 72 Splenomegalies
 - 73 Abnormal constituents of blood used as diagnoses
 - 74-78 Blank
 - 79 Miscellaneous
- 8 blank to 89 *Diseases of vascular and lymphatic system (except 3 blank to 59)*
- 8 (blank) Aneurism and aortitis
 - 80 Arteriosclerosis and senility (except 240)
 - 81 Hypertension and hypotension
 - 82 Phlebitis, thrombosis and varicosities
 - 83 All other diseases of arteries
 - 84 All other diseases of veins
 - 85 Diseases of lymphatic system (including lymph nodes and thymus)
 - 86 Vasomotor and trophic disturbances
 - 87-88 Blank
 - 89 Miscellaneous
- 9 blank to 99 *Diseases of heart (except 13, 14, 3 blank to 59 21 blank, 211 and 27 blank)*
- 9 (blank) Diseases of myocardium (including myocarditis, myocardial insufficiency, cardiac pain and others)
 - 90 Diseases of pericardium (including pericarditis, adherent pericardium)
 - 91 Diseases of endocardium (including endocarditis, valvular lesions, acute and chronic)
 - 92 Cardiac failure from any cause
 - 93 Arrhythmias
 - 94 Cardiac neuroses and neurocirculatory asthenia
 - 95-98 Blank
 - 99 Miscellaneous
- 10 blank to 109 *Diseases of nose, throat, mouth and pharynx (except 0 blank, 04, 06, 07, 11 16 19, 3 blank to 59 and 27 blank)*
- 10 (blank) Diseases of nose and accessory sinuses
 - 100 Diseases of tonsil and adenoid tissue
 - 101 Dental, gingival conditions and lips
 - 102 Diseases of tongue, salivary glands and palate
 - 103 Diseases of pharynx
 - 104-108 Blank
 - 109 Miscellaneous
- 11 blank to 119 *Diseases of esophagus, stomach and duodenum (except 3 blank 59 and 27 blank)*
- 11 (blank) Diseases of esophagus, stomach and duodenum
 - 110 Abnormal stomach contents including observations on acidity
 - 111 Peptic ulcer
 - 112 Functional dyspepsias of all types
 - 113 Other diseases of stomach
 - 114 Other diseases of duodenum
 - 115-118 Blank
 - 119 Miscellaneous

12 blank to 139 *Diseases of intestines, colon, rectum, anus, peritoneum and abdominal viscera (except 00, 09, 10, 15, 3 blank to 59 and 27 blank)*

- 12 (blank) Appendicitis (acute and chronic)
- 120 Obstruction and perforation (including ileus)
- 121 Enterocolitis (acute and chronic)
- 122 Diseases of peritoneum
- 123 Ascites and adhesions
- 124 Constipation
- 125 Diarrhea
- 126 Local rectal and anal conditions (including fistulae, fissures and hemorrhoids)
- 127 Diseases of gallbladder and biliary tract (including cholecystitis and cholelithiasis)
- 128 Diseases of liver
- 129 Jaundice
- 130 Diseases of pancreas (except 6 blank)
- 131 Diseases of spleen (except 72)
- 132-138 Blank
- 139 Miscellaneous

14 blank to 149 *Diseases of respiratory system (except 0 blank, 04, 11, 12, 16, 19, 3 blank to 59)*

- 14 (blank) Diseases of larynx
- 140 Diseases of bronchi (such as bronchitis, bronchiectasis)
- 141 Bronchial asthma and hay-fever
- 142 Foreign bodies
- 143 Diseases of pleura (such as pleurisy, thickened pleura and empyema)
- 144 Other diseases of lungs
- 145-148 Blank
- 149 Miscellaneous

15 blank to 169 *Diseases of urinary tract (except 03, 3 blank to 59 and 27 blank)*

- 15 (blank) Nephritis
- 150 Uremia
- 151 Pyelitis and pyelonephritis (including hydronephrosis and stricture)
- 152 Cystitis
- 153 Other infections and fistulae in urinary tract (including perinephritic abscess)
- 154 Abnormalities of urine used as diagnosis
- 155 Disturbances in flow of urine (such as enuresis, anuria)
- 156 Other disturbances of kidney
- 157 Other disturbances of ureter
- 158 Other disturbances of bladder
- 159 Other disturbances of urethra (except gonorrhea)
- 16 (blank) Postoperative conditions
- 160-168 Blank
- 169 Miscellaneous

17 blank to 179 *Diseases of male reproductive system (except 03, 3 blank to 59 and 27 blank)*

- 17 (blank) Diseases of epididymis and spermatic cords
- 170 Diseases of testis (including orchitis)

- 171 Diseases of scrotum (such as hydrocele, varicocele, spermatocele)
- 172 Diseases of penis (such as redundant prepuce, chancroid)
- 173 Disease of prostate and seminal vesicles (such as prostatic hypertrophy, prostatitis, periprostatic abscess)
- 174 General (including impotence, premature ejaculation, neuroses)
- 175-178 Blank
- 179 Miscellaneous
- 18 blank to 189 *Diseases of female reproductive system (except 03, 3 blank to 59 and 27 blank)*
- 18 (blank) Diseases of vagina and genitalia
- 180 Diseases of uterus
- 181 Diseases of tubes
- 182 Diseases of ovaries
- 183 Abnormalities of pelvic floor
- 184 Pelvic peritoneum (including inflammation, adhesions, abscess and others)
- 185 Abnormalities in menstruation
- 186 General (including neuroses)
- 187-188 Blank
- 189 Miscellaneous
- 19 blank to 199 *Special abnormalities or diseases associated with pregnancy (except 14, 3 blank to 59 and 26 blank to 269)*
- 19 (blank) Abnormal pelvis
- 190 Normal pregnancy
- 191 Toxemias of pregnancy (including pernicious vomiting, eclampsia and others)
- 192 Abortions and premature labor
- 193 Complications of labor
- 194 Complications of puerperium
- 195-198 Blank
- 199 Miscellaneous
- 20 blank to 209 *Diseases of skin, hair and nails (except 0 blank, 01 to 03, 06 to 10, 14, 15, 17 to 19, 3 blank to 59, 82 to 86, 21 blank to 219, 264, 27 blank and 28 blank to 289)*
- 20 (blank) Cocogenous infections (including impetigo, ecthyma, furuncles, carbuncles, abscess, folliculitis, sycosis vulgaris and acne vulgaris)
- 200 Toxic dermatitis (including toxic erythemas, erythema multiforme, erythema nodosum, urticarias, occupational dermatitis, drug sensitizations)
- 201 Mycoses, trichophyton group (including favus, versicolor, epidermymycosis)
- 202 Inflammatory diseases (etiology unknown or uncertain, including psoriasis, pityriasis rosea, eczemas, lichen planus, herpes zoster, herpes simplex, pemphigus, seborrhea)
- 203 Hypertrophies and atrophies (including clavus, callositis, verruca, ichthyosis, vitiligo, keloid)
- 204 Dermatitis venenatas and dermatitis of external causes (including plants in general, paints, phosphorus and roentgen ray or radium)
- 205-208 Blank
- 209 Miscellaneous

- 21 blank to 219 *Diseases of ductless glands exclusive of spleen (except 3 blank to 69 and 17 blank to 189)*
- 21 (blank) Hypert thyroidism (including goiter, toxic adenomas, thyroiditis)
 - 210 Myxedema, cretinism and low basal metabolic rates
 - 211 Simple and colloid goiters
 - 212 Diseases of pituitary
 - 213 Other endocrine disturbances
 - 214-218 Blank
 - 219 Miscellaneous
- 22 blank to 229 *Diseases of eye (except 03, 06, 3 blank to 59, 264 and 27 blank)*
- 22 (blank) General
 - 220 Lids and lacrimal apparatus
 - 221 Conjunctiva
 - 222 Cornea (such as pterygium)
 - 223 Anterior chamber and sclera
 - 224 Errors in refraction
 - 225 Lens retina and optic nerve (such as vision blindness, optic neuritis)
 - 226 Uveal tract, iris, ciliary body, choroid and vitreous
 - 227 Eyeball, orbit, disturbances of motion
 - 228 Blank
 - 229 Miscellaneous
- 23 blank to 239 *Diseases of ear (except 3 blank to 59, 264 and 27 blank)*
- 23 (blank) General
 - 230 Auricle
 - 231 External and auditory canal
 - 232 Eustachian tube
 - 233 Middle ear and mastoid cells
 - 234 Internal ear—semicircular canals
 - 235 Internal ear—cochlea
 - 236 Special disturbances in hearing
 - 237-238 Blank
 - 239 Miscellaneous
- 24 blank to 259 *Diseases of nervous system (except 0 blank to 59 and 26 blank to 269)*
- 24 (blank) Multiple sclerosis
 - 240 Arteriosclerosis of the central nervous system
 - 241 Congenital and familial disease
 - 242 Progressive muscular dystrophy and myasthenia gravis
 - 243 Hyperkinetic diseases (such as chorea, paralysis agitans, tics, epidemic encephalitis)
 - 244 Head injuries involving brain
 - 245 Spinal injuries involving cord
 - 246 Neuralgias and neuritis
 - 247 Migraine
 - 248 Epilepsy and epileptiform convulsions
 - 249 Other general diseases of central nervous system
 - 25 (blank) Other diseases of meninges
 - 250 Other diseases of brain
 - 251 Other diseases of cranial nerves
 - 252 Other diseases of peripheral nerves

- 253 Other diseases of spinal cord
- 254-258 Blank
- 259 Miscellaneous
- 26 blank to 269 *Abnormal mental conditions*
 - 26 (blank) Organic conditions (except 3 blank to 39 and 24 blank to 259)
 - 260 Dementia praecox group
 - 261 Manic depressive group
 - 262 Mental deficiency
 - 263 Constitutionally psychopathic personalities
 - 264 Minor psychoses (including hysterias, traumatic and occupational neuroses, except 94, 112, 174, 186)
 - 265 Environmental maladaptations (including all types of mental conflicts)
 - 266 Symptomatic conditions (including deliriums and coma)
 - 267-268 Blank
 - 269 Miscellaneous
- 27 blank to 279 *Constitutional and developmental abnormalities*
 - 27 (blank) Congenital abnormalities (except 32, 35, 241)
 - 270 Defective physical development
 - 271 Fetal monstrosities
 - 272-278 Blank
 - 279 Miscellaneous
- 28 blank to 289 *Environmental causes of injury and disease*
 - 28 (blank) Physical environmental conditions (including heat, sun, exposure, light, dust and humidity)
 - 280 Poisonings (including food, drugs, serum sickness)
 - 281 Alcoholism and drug addiction
 - 282 Wounds, abrasions, contusions, bruises, sprains
 - 283 Dislocations
 - 284 Fractures
 - 285 Burns
 - 286-288 Blank
 - 289 Miscellaneous
- 29 blank to 299 *Bones, muscles, fascia and locomotor system in general (except 03, 14, 3 blank to 59, 28 blank to 289 and 31 blank to 319)*
 - 29 (blank) Bone deformities (including osteomyelitis, periostitis and others)
 - 290 Bone diseases (including osteomyelitis, periostitis and others)
 - 291 Other bone abnormalities and diseases
 - 292 Diseases of joints (including arthritis and ankylosis)
 - 293 Diseases of muscles (except 242)
 - 294 Diseases of fascia and tendons (including cellulitis)
 - 295 Diseases of bursae
 - 296-298 Blank
 - 299 Miscellaneous
- 30 blank to 309 *Miscellaneous medical conditions or diseases*

UNASSIGNED

- 31 blank to 319 *Miscellaneous surgical conditions or diseases*
 - 31 (blank) Inguinal and femoral hernias
 - 310 Other types of hernias
 - 311 Gangrenes, all types

| | |
|-----------------|---|
| 312-318 | Blank |
| 319 | Miscellaneous |
| 32 blank to 329 | <i>Special pediatric and child-welfare conditions</i> |
| 32 (blank) | Stillborns |
| 320-328 | Blank |
| 329 | Miscellaneous |
| 33 blank to 389 | <i>(Six unassigned major subdivisions)</i> |
| 39 blank to 399 | <i>Miscellaneous</i> |
| 39 blank to 398 | Blank |
| 399 | Miscellaneous |

In case most of the records of an institution belong to some special service, it would be desirable to code this particular section of the diagnostic code to the third column. For example, let us consider a set of records made up of dermatologic patients. The special section for skin is from 20 blank to 209. Each of these eleven headings can be subdivided by the third column into eleven subheadings, making one hundred and twenty-one possibilities in this section. But dermatologic observations would also be listed in other sections of the diagnostic code: one or two under 0 blank, about five under 01, from five to eight under 09, eleven under 33, eleven under 44, eleven under 52, from five to ten under 21 blank to 219, from ten to twenty under 27 blank to 279, eleven under 282, eleven under 285 and eleven under 311, a total of at least 200 subdivisions.

There are six major headings, 33 blank to 389, which are unassigned, each containing 121 possible entries. Any or all of these could be used for dermatology if desired. By this means the diagnostic code has been kept elastic, permitting the assignment of code divisions according to the major interests in the hospital.

Code for Age—The code for age occupies columns 22 and 23. Birth is represented by 00 and the years from 1 to 98 by the identical number on the card. Number 99 indicates 99 years and over. Column 23 is used a second time for age in the first year by the blank position being punched instead of the zero in column 22. This distinguishes the unit numbers from 0 to 9 in column 23 as to whether they are preceded by a zero or a blank. The first year of age is coded as follows: blank 0, under 1 week of age, except new-born, blank 1 from 1 to 2 weeks, blank 2, 2 to 3 weeks, blank 3, 3 weeks to 1 month, blank 4, 1 to 2 months, blank 5, 2 to 3 months, blank 6, 3 to 4 months, blank 7, 4 to 6 months, blank 8, 6 to 9 months, and blank 9, from 9 to 12 months.

Code for Sex and Color—The code for this is indicated in column 24. Male white is indicated by 0, male black by 1, female white by 2, female black by 3, and information on sex or color unknown or not recorded by 4.

Code for Civil State and Outcome—In order to save space, it was necessary to code civil state and outcome together in column 25 by a combination code. Both civil state and outcome are divided into three parts. Code no 0 signifies outcome well, civil state single, no 1, outcome well, civil state married, no 2, outcome well, civil state divorced, widowed or separated, no 3, outcome dead, civil state single, no 4, outcome dead, civil state married, no 5, outcome dead, civil state divorced, widowed or separated, no 6, outcome improved, same or worse, civil state single, no 7, outcome improved, same or worse, civil state married, no 8, outcome improved, same or worse, civil state, divorced, widowed or separated. The code number for column 25, therefore represents one of the nine possible combinations between the two items of outcome and civil state. In the illustrative diabetic case, civil state is recorded as married, outcome improved, and it therefore is indicated by a code number 7 in column 25.

Code for History, Columns 26 to 29—The code for the history is as follows:

(a) Past illness column 26 (including weight curve fig 1 p 6) 1, typhoid to scarlet fever, 2, syphilis and gonorrhea and abnormal weight curve, 3, accidents and operations, 4, operations on the nose and throat, 5, miscellaneous past illnesses not included in 1 to 4.

(b) Respiratory, circulatory and gastro-intestinal systems, column 27 1, respiratory system, 2 circulatory system, 3, gastro-intestinal system,—appetite to jaundice, 4, gastro-intestinal system, remaining items, 5, miscellaneous items for respiratory, circulatory and gastro-intestinal systems, not listed under 1 to 4.

(c) Genito-urinary and nervous systems, column 28 1, Genito-urinary system, 2, nervous system, sense of exhaustion to mental conflicts, 3, nervous system, ear, 4, nervous system, eye, 5, miscellaneous under genito-urinary and nervous systems not included in 1 to 4.

(d) Family history, marital history, menstrual history, habits and inaccuracy of history, column 29, 1, family history, 2, marital history, 3, menstrual history, 4, habits, and 5, inaccuracy of history.

Code for Body Weight—Body height is coded in inches in column 30, blank, unknown, 0, under 24, 1, from 24 to 29, 2, 30 to 35, 3, 36 to 41, 4, 42 to 47, 5, 48 to 53, 6, 54 to 59, 7, 60 to 65, 8, 66 to 71 and 9 72 and over. Mrs H Brown had a height of 64 inches indicated by a code number of 7 in column 30.

Code for Body Weight—The code for body weight is indicated in column 31 in pounds, blank unknown 0, under 20 1, from 20 to 39, 2 40 to 59, 3, 60 to 79 4 80 to 99 5, 100 to 129, 6, 130 to 159 7 160 to 189, 8 190 to 219 and 9 220 and over. Mrs H Brown had a body weight of 160 pounds which is indicated by a code number of 7 in column 31.

Code for Physical Examination, Columns from 32 to 39—The code for the physical examination follows

(a) Abnormalities in temperature and abnormalities of the head and face are coded in column 32 1, temperature, 2, head and face, hair to eyes, 3, head and face, ears, 4, head and face, nose and jaw, and 5, miscellaneous under head and face not listed under 2, 3 and 4

(b) Abnormalities of the mouth and throat, column 33 1, lips, gums and teeth, 2, tongue, palate and pharynx, 3, tonsils, 4, larynx, and 5, miscellaneous under mouth and throat, not included in 1 to 4

(c) Abnormalities of the neck, spine and thorax, column 34 1, neck, 2, spine, 3, general respiratory tract and breast, 4, inspection of thorax, and 5, miscellaneous items under neck, spine and thorax, not included in 1 to 4

(d) Abnormalities of the chest and lungs, column 35 1, inspection, 2, tactile fremitus and percussion, 3, abnormal breath sounds, whispered voice and spoken voice, 4, râles and friction rub, and 5, miscellaneous under chest and lungs not recorded in 1 to 4

(e) Abnormalities of the heart and rate of heart, column 36 1, inspection and palpation, 2, percussion and abnormal outline of heart, 3, auscultation, 4, rate of heart at apex and pulse, and 5, miscellaneous abnormalities of heart not listed under 1 to 4

(f) Abnormalities of the vessels and abdomen, column 37 1, vessels, 2, inspection of abdomen, 3, palpation of tenderness, rigidity and abdominal organs, 4, palpation of mass and inguinal rings, and 5, miscellaneous under abdomen not included in 1 to 4

(g) Abnormalities of the extremities and neurologic symptoms, column 38 1, club digits to varicose ulcer, 2, motor, 3, joints, 4, neurological, and 5, miscellaneous under extremities and neurological not included in 1 to 4

(h) Abnormalities of the lymph nodes, skin, genitalia, rectum and psyche, column 39 1, lymph nodes, 2, skin, 3, genitalia, 4, rectum, and 5, psyche The miscellaneous of the various groups in this section are included with the respective subdivisions

Code for Laboratory Observations, Columns 40 to 43—The code of laboratory observations follows

(a) Abnormalities in the examination of urine, blood, Wassermann reaction, spinal fluid, sputum, throat culture, blood culture and Widal, column 40 1, indicates urine, 2, blood from hemoglobin to white blood cell count, 3, blood from platelets to comment, 4, Wassermann and spinal fluid, and 5, sputum, throat culture, blood culture and Widal

(b) Abnormalities of the following, column 41 1, signifies blood chemistry, 2, basal metabolic rate and electrocardiograph report, 3, cystoscopic and phthalein examination, 4, proctoscopic, stool and fractional test meal, and 5, examination of the ear, nose and throat

(c) Abnormalities of roentgen-ray and dental examination, column 42 1, roentgen-ray examination of the head, neck and thorax, 2, of skeleton spine, extremities and pelvis, 3, of gastro-intestinal tract, 4, of abdominal viscera, urinary system and miscellaneous, and 5, dental examination, including roentgen-ray of teeth

(d) Abnormalities in examination of the eye and miscellaneous laboratory tests, column 43 1, examination of the eye, 2 and 3, laboratory tests, beginning with letters a to l, 2, normal, 3, abnormal, and 4 and 5, laboratory tests, m to z, 4, normal, 5, abnormal

There are probably from 100 to 200 miscellaneous laboratory tests. It is considered desirable to split this total number into two parts, and this is accomplished alphabetically. The first letter in the technical name of the test is used for the purpose. For example, if a patient should have a sugar tolerance test that was abnormal it would be coded as item 5, column 43. If the test was normal, it would be represented by code no. 4.

Code for Miscellaneous, Columns 44 and 45—Columns 44 and 45 permit space for listing ten abnormalities in which the institution or the physician is especially interested. We suggest the following uses for these two columns:

In column 44, 1, signifies autopsy, 2, a major operation, 3, a minor operation on the nose or throat or a dental extraction, and 4, previous admissions. Columns 45 may be retained as a service column to indicate the principal service on which a patient is examined and treated. At least five services would be required by almost all hospitals, namely—medicine, surgery, gynecology, obstetrics and pediatrics. Other subdivisions about twenty in all could be noted. The coding would be as follows: 00, medicine, 01, medicine and some other service, 02, surgery, 03, surgery and some other service, 04, gynecology, 05, gynecology and some other service, and so on. The even numbers could be listed up to twenty different services, and the odd numbers could be retained for patients in these respective services who were also treated in some other hospital service.

DESCRIPTION OF THE TECHNIC OF PUNCHING CARDS AND WHAT IT MEANS TO THE RECORD DEPARTMENT OF THE AVERAGE HOSPITAL

The machine used to punch the index card is simple in construction and easy to use (fig. 7). This machine and a few filing boxes represent the only special equipment necessary for the installment of the index in the average hospital. Punch machines can be rented by the month from both the Powers and International Tabulating Machine Companies or the hand instrument of the type in the diagram can be purchased from the International Time Recording Company. The nonelectrical type of punch machine would be adequate for the needs of all smaller hospitals.

The punch card is placed on a moving platform as observed in figure 7. The keys are struck one at a time for any desired number. As the

key is punched, the machine automatically moves the card to the next column. Its action in this respect is similar to that of a typewriter.

The safest way to check the punch card is to have the clerk punch a set of cards and then punch a second set from the same original observations. If the corresponding cards in the two sets are superimposed and held to the light, a glance is sufficient to see that all the holes are punched similarly. This process reduces the error due to the personal equation to an extremely low probability.

A filing clerk can be trained to carry on this system in about two weeks' time. An expert can punch about 2,000 cards during an eight hour day. A clerk of average ability will have no difficulty in coding, punching and checking at least 100 cards a day. This is an average daily discharge rate greater in magnitude than any except that of the largest hospitals in the country.

It will be necessary for the hospital to provide from three to four filing boxes to keep these punch cards for a period of from six months to a year. One box will hold from 1,500 to 2,000 cards.

DESCRIPTION OF THE PRINTED CROSS-INDEX

After the punch cards have accumulated for three, six or twelve months, they are sent away and made up into a printed cross-index. The index cards described for this system were designed for the Powers Printing Tabulator. Cards might be equally well designed for the International Tabulating Machine. The printed record which is returned to the hospital will list the information on these index cards in every desired fashion, so that it is unnecessary to keep the cards after the printed record has been returned.

The description of this printing process does not concern the hospital. The printed record which is returned to the hospital is in the form of a loose-leaf, postbound index. A page will be set aside in this index for each of the various diagnoses and the major divisions in the history, physical examination and laboratory observations. For example, figure 8 shows a sample page, entitled diabetes mellitus, the fifth printed line of figures on this page represents the complete index record of the illustrative diabetic case of Mrs. H. Brown. Every coded item on her index card (fig. 6) is printed on this one line of type. This same line of type signifying all the important facts about the case will be printed on thirty other pages in the cross-index. It will appear on all of the pages entitled with the abnormalities which are indicated as positive for her case. For instance, it will be listed on the pages entitled obesity, acidosis, arteriosclerosis, hypertension, constipation, hemorrhoids, positive items 1, 2, 3 and 4 from past illness, positive respiratory history, positive circulatory history, abnormal gastro-intestinal history, item 4.

abnormal nervous system history item 2 abnormal family history, abnormal observations on the eye and mouth and throat no 2 abnormal observations on the neck, râles and friction rub, abnormal observations on the heart, item 3, abnormal vessels, abnormal observations on the skin, abnormalities of the rectum, abnormalities in psyche, abnormal urine, abnormal blood chemistry, abnormal observations on the ear, nose and throat, abnormal roentgenogram of the head, neck and thorax, abnormal results from dental examination, and abnormal observations following examination of the eye

The physician can turn to any one of these index pages and find the complete entry of all coded facts for the case of Mrs H Brown

For the sake of illustration we have coded the information in several other diabetic cases. The abnormal observations in each case are listed as a single line of type in figure 8. Therefore, if the physician desires

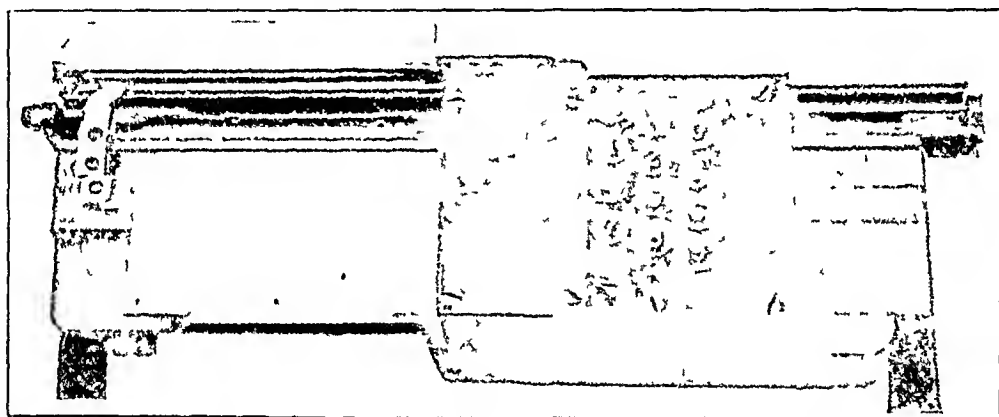


Fig 7—Machine used for the punching of index cards

to obtain the diabetic cases of those patients who also had arteriosclerosis and cardiac symptoms, and who were more than 50 years of age, he would turn to this index page entitled diabetes mellitus in the printed volume and locate the record of those patients who had arteriosclerosis (code no 80), this would involve cases 53123, 59106 and 67190. Of these three patients, a glance at columns 22 and 23 demonstrates that only the first two patients were more than 50 years of age and of these two only one, 59106, in column 36, showed positive cardiac symptoms.

It is planned that these printed cross-index sheets will be bound in loose-leaf volumes and that the volumes will increase in size from year to year as a continuous loose-leaf, postbound index. For example, tabulation of diabetes mellitus for 1927 will immediately follow the diabetic cases for 1926, and in this way all the diabetic cases over the entire period of the hospital record system will be noted in the same position of the cross-index. This is a material advantage, since only one search will be necessary for any given type of abnormal observations.

From six to eight duplicates of the printed index file can be made if desired. This makes it possible for several departments of the hospital, or for hospitals in different parts of the country to have at hand a complete index of all cases in any given institution. Loss or destruction of an index is practically impossible if duplicates are made.

ESTIMATION OF COST OF MECHANICAL INDEX SYSTEM

The cost of this index will vary somewhat with the number of case records involved. Several items enter into the estimate, namely, the purchase or rental of a machine to punch the index cards, the purchase of index cards—which should not amount to more than a few dollars a year for the average hospital—the wages of a clerk for from one-half to full time depending on the size of the hospital and the efficiency

| Case Number | Diagnoses | | | | | | | | | Age | Sex | Color | Qts AC1 & 8 | History | | | | Height | Weight | Physical Exam | | | | | | Laboratory | | | Misc | | | |
|-------------|-----------|-----|-----|-----|-----|-----|-----|----|----|-----|-----|-------|-------------|-----------|---------|------------------|----------|--------|--------|---------------|------|------|---------------|--------------|-------------|-----------------|----------------|---------|------|---------|---------|---------|
| | #1 | #2 | #3 | #4 | #5 | #6 | #7 | #8 | #9 | | | | | Post Ill. | R C AC1 | Q.U. AC1 | Routine | | | T. Hands | Feet | Neck | Chest & Lungs | Heart & Rate | Yes Abdomen | Extrem. & Neur. | LN SK G R & F. | Col. 10 | | Col. 11 | Col. 12 | Col. 13 |
| 018073 | 6b | 100 | 266 | | | | | | | 19 | 2 | 0 | 03070100 | 8 | 5 | 001001000010002 | 01050000 | 0300 | | | | | | | | | | | | | | |
| 053123 | 6b | 013 | 080 | 311 | | | | | | 67 | 1 | 5 | 01160100 | 9 | 7 | 000001300011100 | 01071201 | 0600 | | | | | | | | | | | | | | |
| 059106 | 6b | 04b | 080 | 081 | 101 | 216 | | | | 51 | 1 | 6 | 16010100 | 8 | 7 | 020111010000101 | 01010500 | 0000 | | | | | | | | | | | | | | |
| 061331 | 6b | 060 | 121 | 127 | 20b | | | | | 45 | 2 | 1 | 07260126 | 7 | 8 | 000200000030010 | 06010300 | 0200 | | | | | | | | | | | | | | |
| 067190 | 6b | 060 | 053 | 080 | 081 | 121 | 126 | | | 49 | 2 | 7 | 26170201 | 7 | 7 | 0202010103010021 | 01090901 | 0000 | | | | | | | | | | | | | | |
| 070125 | 6b | 070 | 127 | 13b | | | | | | 39 | 0 | 8 | 10070017 | 8 | 8 | 0006170000130000 | 17010000 | 0000 | | | | | | | | | | | | | | |

Fig 8—Sample page labeled diabetes mellitus from the printed cross index. The information given on index card, figure 6, appears as the fifth printed line of type.

of the clerk, the purchase of from two to eight boxes as a temporary file for punch cards and the cost of the printed cross-index.

The printing of the cross-index represents the only formidable item in this list. If a number of hospitals accepted the same index set-up, the price for each would be considerably reduced. It would be possible to reduce this expense to a great degree if some medical institution would rent a set of tabulating machinery and make up the printed cross-indexes for a dozen or more hospitals. The total expense for the printing could then be divided and would become a minor consideration in the sums allotted the record department.

It is probable that the installation of this mechanical index-system would release some clerical expense and save considerable time involved at present in the search for records. We believe, although we have not been able to test the matter by actual trial, that the expense

involved in the system would be equal approximately to that of maintaining the present average cross-index and that it would not be an excessive burden even if it were superimposed on an existing system

SUMMARY OF ARGUMENTS IN FAVOR OF THE MECHANICAL CROSS INDEX

The mechanical cross-index, as here outlined, fulfils the features that seem to be desirable for a hospital index

- 1 It would be possible to locate the case number of records desired by the physician within a few minutes' time regardless of inaccurate information in respect to the patient's name

- 2 It would do away with misplacement of records due to multiple or ambiguous diagnoses

- 3 It permits the location of records by history and physical examination as well as by diagnoses

- 4 It fills the need of a small hospital with about the same efficiency that it does a larger institution

- 5 It is elastic, and can be adapted to any type of special interest in medical work

- 6 After the coding is understood and the routine established one clerk can handle the entire index system regardless of the size of the hospital

- 7 The expense approximates the present outlay for the average cross-index in use by most hospitals. It must be realized in this connection that the cost of such an index would be prohibitive unless a systematic case record form of the general type proposed in this article is used. In the ordinary case history now in vogue in hospital practice, the coding feature would be a major consideration, and an almost insurmountable barrier

CHRONIC SPLENOMEGALY ¹

WILLIAM CARPENTER MACCARTY, M D

ROCHESTER, MINN

During the last twenty-five years, surgeons have attempted to add surgical treatment to other forms of therapy in many conditions characterized by anemia and splenomegaly. They have, therefore, applied splenectomy in advanced, and in some early, cases of splenic anemia, hepatic cirrhosis, hemolytic icterus, pernicious anemia, myelogenous leukemia, Gaucher's ¹ disease, and recently, to hemorrhagic purpura. Their efforts have been beneficial in splenic anemia, hemolytic icterus and hemorrhagic purpura, but rather unsatisfactory in pernicious anemia and in myelogenous leukemia. Occasionally splenectomy in hepatic cirrhosis is followed by improvement. Removal of the spleen as a therapeutic procedure has been based on the facts that it may be removed without definite damage to life, that this organ may be a factor in the destruction of blood in some cases of anemia, that any tumor which interferes with the vital functions of other organs should be removed, and that splenectomy empirically performed in hemorrhagic purpura is unquestionably followed by an almost immediate and permanent rise in the blood platelet count with prevention of further purpura. In general, these facts account for the relatively large number of spleens which have been studied in making this series of observations. Heretofore most of the information relative to this organ's normal and abnormal structure and function has been obtained from material observed at autopsy and from experimental animals. It has seemed wise, therefore, to examine those spleens which have been removed at operation.

In reviewing the literature on hematology and the normal structure and function of the spleen, one is impressed principally by the confusion in nomenclature and by the great differences in observations and opinions. An attempt, therefore, has been made to make original observations without being biased by previous reading. The nomenclature for cells is that which I described in 1919 ². At that time all names of adult cells ended in cyte, and all regenerative types of cells in blast, thus the red blood corpuscle was called an erythrocyte and a nucleated red cell (normoblast, etc.) an erythroblast. Instead of using the term myelocyte, the immediate progenitors of the leukocytes were called leukoblasts. A regenerative stage or form of an endotheliocyte was called an endo-

¹ Read before the Section on Pathology and Physiology at the Annual Session of the American Medical Association, Washington, D. C., May, 1927.

² A preliminary report.

1 Gaucher. *Bull et mem Soc med d hop de Paris* **60** 630, 1892.

2 MacCarty, W. C. A Biological Conception of Neoplasia, Its Terminology and Clinical Significance, *Am J M Sc* **157** 657, 1919.

thelioblast This uniformity of terminology has served a useful purpose in the study of the relationship of cells to other cells and of their morphology in relation to biologic behavior Besides the confusion in nomenclature, there has been some difference of opinion in the description of clinical entities which are associated with splenomegaly In the following study, however, the conditions named were typical, and there was never any doubt about the clinical pictures as they have been uniformly accepted

The material investigated was obtained from eighty-two cases of splenic anemia, fifteen of hepatic cirrhosis, fifty of hemolytic icterus, fifty-one of pernicious anemia, thirty of myelogenous leukemia, six of Gaucher's disease, and twenty of hemorrhagic purpura, making a total of 254, to which must be added a miscellaneous group of sixty-six in which the clinical picture was not definite enough to be classified but which was associated with splenomegaly Thus 320 spleens³ were studied with the following ideas in mind

- 1 The establishment of a standard cytology regardless of the confusion in nomenclature

- 2 To determine whether the histologic and cytologic splenic pictures bear any specific relation to the recognized clinical entities as they are accepted by modern diagnosticians and teachers of medicine

- 3 To determine, if possible, if there might be any relation between the so-called clinical entities

- 4 To obtain any possible information on the normal and abnormal structure and function of the spleen

The normal spleen is a vascular organ in which lymph follicles are extremely numerous, the main problem for all investigators has been the establishment of correct structural relationships between the lymphatic tissues, the supporting network of connective tissue (frequently called the reticulo-endothelial tissue) and the circulating blood Many differences of opinion may be found in the literature, and few, if any, have a perfectly clear idea of the exact structural and functional characteristics of this organ In general, it may be said that the structural and functional unit is a complex one with the germ center at one end and the circulating blood at the other as shown in the illustration Between the two there is a network composed of fibrocytes and their elongated fibrils which form the meshes in which lymphocytes and normal blood cells intermingle in performing the one or more functions of the organ

³ Between 1904 and 1927, 456 splenectomies were performed in the Mayo Clinic The material presented in this study represents only a part, other spleens have been used in the study of circulation by Passalacqua and Gay, and the connective tissue of the organ by Perez Fontana These reports will appear in the near future

Under normal conditions there are certain definite types of cells which are constantly found in the spleen. Thus one sees lymphoblasts, lymphocytes, fibroblasts, fibrocytes, erythrocytes, endotheliocytes and at least two (neutrophilic and eosinophilic) of the recognized leukocytes, basophilic leukocytes are rare and frequently difficult to differentiate

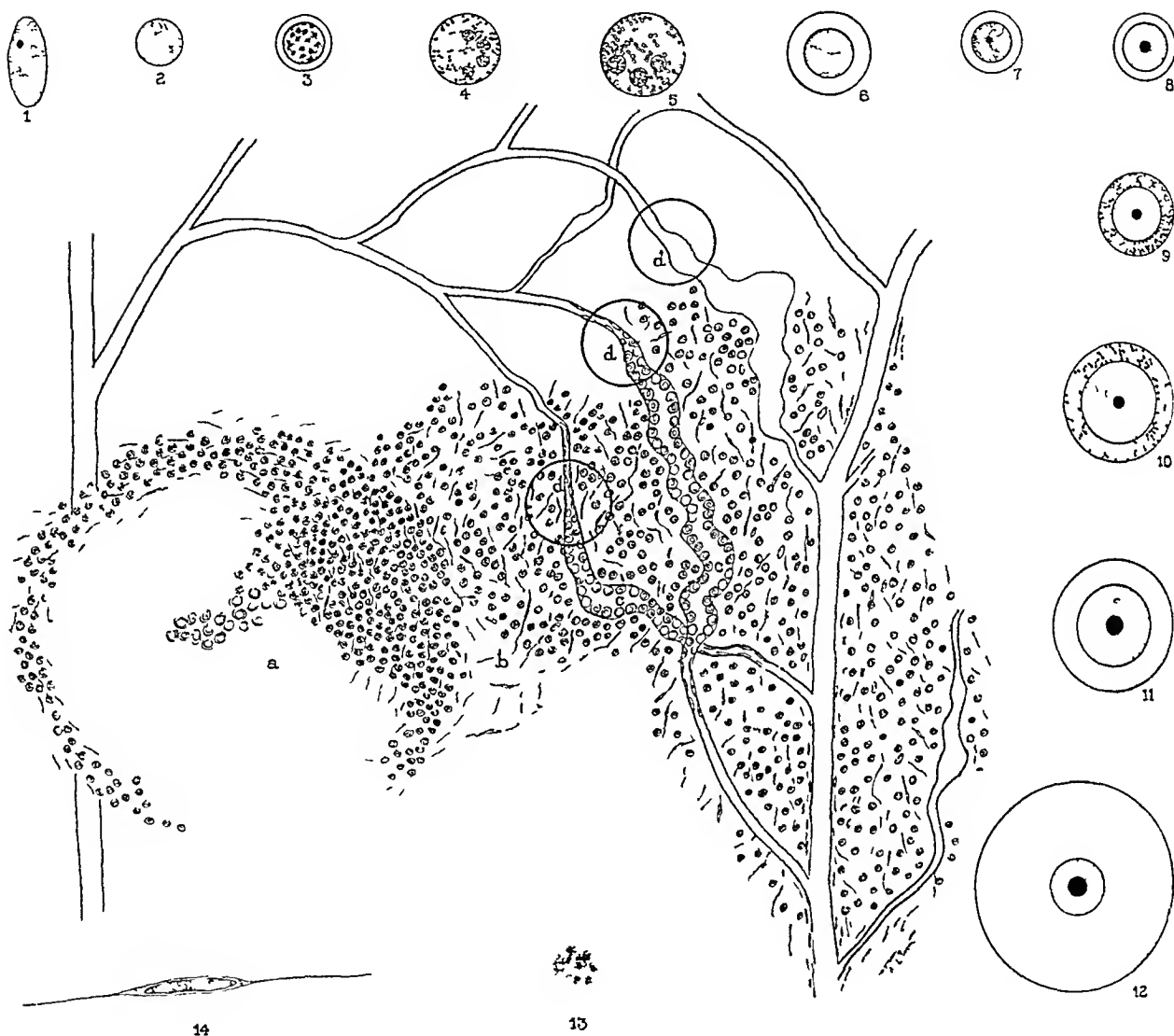


Diagram of histologic and cytologic units of the normal spleen and the cells found under pathologic conditions. *a* shows the germ center in lymph follicle, *b*, reticulum containing lymphocytes, fibrocytes and fibroblasts, *c*, the sinuses, and *d*, the disputed area in which arterial capillaries enter sinuses (Do they become dilated into sinuses, or do they enter at stoma in the endothelial walls of sinuses?). All cells are drawn to scale from unembedded fresh material. They are as follows: 1 is a fibroblast, 2, erythrocyte, 3, lymphocyte, 4, neutrophilic leukocyte, 5, eosinophilic leukocyte, 6, endotheliocyte, 7, erythroblast, 8, lymphoblast, 9, small neutrophilic leukoblast, 10, eosinophilic leukoblast, 11, endothelioblast, 12, Gaucher cell, 13, pigment and 14, fibrocyte.

positively from eosinophilic leukocytes, in my own studies they have been too few and uncertain to allow any conclusions relative to them and their possible relation to the subject. Under abnormal conditions such as exist in the clinical entities of this study, one sees not only quantitative proportional variations in the types of cells which are normally present, but also the presence of the younger forms—the blasts of the normal cells, as shown in the illustration. In addition one sees in varying degrees deposits of pigment which are a residue of erythrocytes which have been destroyed either in the circulating blood or in the spleen itself. The changes which one sees in splenomegaly are relative and have to do with changes in the organ dependent on the relative presence of normal cells, young cells, pigment, changes in the network of the connective tissue, obstruction to the flow of blood and reduction of normal structural units. The idea that the spleens, which are a part of each clinical entity, possess characteristic changes which differ from other clinical entities is incorrect, as will be seen in the accompanying figures. I shall consider each clinical entity separately and briefly state the things which make it an entity and then describe the conditions of the spleens.

CLINICAL ENTITIES

Splenic Anemia (Banti's Disease)—There may be some question as to whether Banti's disease is always splenic anemia or whether splenic anemia is always that picture which Banti⁴ described. In the one, enlargement of the spleen is subsequently followed by cirrhosis of the liver, in the other, the spleen is enlarged without demonstrable cirrhosis of the liver. In both conditions, there is anemia without apparent changes in the morphology of the erythrocytes. Whether or not Banti's disease and splenic anemia are the same disease, both are accompanied by splenic enlargement and anemia with the other clinical conditions which accompany anemia. The spleens are grossly and microscopically indistinguishable, one from the other. For practical purposes, the two diseases are usually considered as one. In this series, the facts shown in table 1 were noted.

The most obvious things in the spleens in cases of advanced splenic anemia are the great size of the organ, replacement of pulp by dense connective tissue, relative reduction of the number of germ centers, dilatation of the sinuses and the presence of pigment which is, however, much less in amount than that found in pernicious anemia and hemolytic icterus. The cells lining the sinuses are usually small compared with those of the normal sinuses. The spleens in splenic anemia are the largest spleens in this series of conditions.

4 Banti. Ziegler's Beiträge, vol. 24

Hemolytic Icterus—This is perhaps a less definite and less easily recognized clinical entity than splenic anemia. It usually occurs in younger persons and even in infants. The typical picture is characterized by enlargement of the spleen, some enlargement of the liver, moderate

TABLE 1—Data for Patients with Splenic Anemia*

| | |
|--|----------|
| Average age of patient | 33 years |
| Percentage males | 58 |
| Percentage palpable spleens | 94 |
| Average weight of spleen | 1,040 Gm |
| Percentage showing congestion in spleen | 0 |
| Percentage showing pigment in spleen | 62 |
| Percentage showing leukocytes (neutrophilic) in spleen | 67 |
| Percentage showing leukocytes (eosinophilic) in spleen | 41.5 |
| Percentage showing germ centers in spleen | 28.1 |
| Percentage showing lymph follicles in spleen | 85 |
| Percentage showing thickened blood vessels in spleen | 65 |
| Percentage showing hyalinized blood vessels in spleen | 25 |
| Percentage showing fibrocytes | 78 |
| Percentage showing fibroblasts | 90 |
| Percentage showing atrophic endotheliocytes | 68 |
| Percentage showing normal endotheliocytes | 56 |
| Percentage showing endothelioblasts | 25 |
| Percentage showing leukoblasts (myelocytes) | 13.5 |

* *Technic*—Blocks were taken from different parts of each spleen and studied in the fresh unfixed and fixed condition without any form of embedding. Notes on all slides were made according to a definite cytologic morphologic standard without any regard to the clinical diagnosis. They were later studied together. The percentages are only relative when comparing one disease with another, they do not represent the exact frequency of the various factors in the different disease entities, because complete serial sections were not made through all spleens.

TABLE 2—Data for Patients with Hemolytic Icterus

| | |
|--|-----------|
| Average age of patient | 27.5 yrs. |
| Percentage of males | 49 |
| Percentage palpable spleens | 88 |
| Average weight of spleen | 850 Gm |
| Percentage showing congestion in spleen | 60 |
| Percentage showing pigment in spleen | 96 |
| Percentage showing leukocytes (neutrophilic) in spleen | 32 |
| Percentage showing leukocytes (eosinophilic) in spleen | 44 |
| Percentage showing germ centers in spleen | 17 |
| Percentage showing lymph follicles in spleen | 80 |
| Percentage showing thickened blood vessels in spleen | 32 |
| Percentage showing hyalinized blood vessels in spleen | 8 |
| Percentage showing fibrocytes | 17 |
| Percentage showing fibroblasts | 52 |
| Percentage showing atrophic endotheliocytes | 41 |
| Percentage showing normal endotheliocytes | 65 |
| Percentage showing endothelioblasts | 34 |
| Percentage showing leukoblasts (myelocytes) | 11 |

anemia, increased erythrocytic fragility and an icteric tint to the skin. The condition is frequently differentiated with difficulty from biliary obstruction and pernicious anemia. In this series of fifty cases, the observations contained in table 2 were noted.

Pernicious Anemia—This condition presents an anemia with a low erythrocytic count and a low percentage of hemoglobin plus variation in size, and irregularity in the shape of the erythrocytes associated with the presence of erythroblasts. Other manifestations and sequelae of anemia are frequently present. The disease is not characterized by excessive splenic enlargement, although the spleen was palpable in 45 per cent of this series of fifty-one cases. The condition has been considered a disease of the blood, but since there is an extensive destruction of erythrocytes as well as incompleteness in their production, surgeons have considered the spleen a possible source of erythrocytic destruction. This accounts for the experimental period in which splenectomy was tried as a possible good therapeutic procedure. The results have been discouraging, and one now rarely has the opportunity to see spleens of

TABLE 3—Data for Patients with Pernicious Anemia

| | |
|--|----------|
| Average age of patient | 47 years |
| Percentage of males | 73 |
| Percentage of palpable spleens | 45 |
| Average weight of spleen | 350 Gm |
| Percentage showing congestion in spleen | 37 |
| Percentage showing pigment in spleen | 96 |
| Percentage showing leukocytes (neutrophilic) in spleen | 55.5 |
| Percentage showing leukocytes (eosinophilic) in spleen | 69.5 |
| Percentage showing germ centers in spleen | 11 |
| Percentage showing lymph follicles in spleen | 97 |
| Percentage showing thickened blood vessels in spleen | 48 |
| Percentage showing hyalinized blood vessels in spleen | 44 |
| Percentage showing fibrocytes | 16 |
| Percentage showing fibroblasts | 43.5 |
| Percentage showing atrophic endotheliocytes | 26 |
| Percentage showing normal endotheliocytes | 63 |
| Percentage showing endothelioblasts | 45 |
| Percentage showing leukoblasts (myelocytes) | 49 |

patients with pernicious anemia until after the inevitable death. The data for these patients are given in table 3.

The spleens of patients with pernicious anemia are not any more characteristic than those of patients with hemolytic icterus, and both have some things in common. In both there is a large amount of pigment, this is much greater than is found in any other splenic condition in this series. In pernicious anemia the disease is apparently one which manifests itself in the spleen by erythrocytic destruction, pigmentation, and the increased presence of leukocytes and leukoblasts. There is an apparent increase in the presence of endothelial regeneration in the sinuses manifested by endothelioblasts. Chronicity is not so evident, as may be seen in the apparent absence of connective tissue proliferation, although there is evidence of its early stages as seen in the increase in the number of fibroblasts. The blood vessels show an unusual amount of hyalinization and thickening.

Myelogenous Leukemia—The condition in myelogenous leukemia is characterized by anemia plus the presence of myelocytes (leukoblasts) in the circulating blood and tissues. It is usually associated with splenic enlargement. For a short period, the patients with the condition were treated empirically by splenectomy, with poor results. In this series, there were thirty spleens which showed the features given in table 4.

TABLE 4—Data for Patients with Myelogenous Leukemia

| | |
|--|----------|
| Average age of patient | 37 years |
| Percentage of males | 31 |
| Percentage of palpable spleens | 100 |
| Average weight of spleen | 830 Gm |
| Percentage showing congestion in spleen | 3 |
| Percentage showing pigment in spleen | 74 |
| Percentage showing leukocytes (neutrophilic) in spleen | 57.5 |
| Percentage showing leukocytes (eosinophilic) in spleen | 38 |
| Percentage showing germ centers in spleen | 7 |
| Percentage showing lymph follicles in spleen | 80 |
| Percentage showing thickened blood vessels in spleen | 35 |
| Percentage showing hyalinized blood vessels in spleen | 3 |
| Percentage showing fibrocytes | 42.5 |
| Percentage showing fibroblasts | 48 |
| Percentage showing atrophic endothelocytes | 32 |
| Percentage showing normal endothelocytes | 44.5 |
| Percentage showing endothelioblasts | 64 |
| Percentage showing leukoblasts (myelocytes) | 71.5 |

TABLE 5—Data for Patients with Cirrhosis and Splenomegaly

| | |
|--|----------|
| Average age of patient | 41 years |
| Percentage of males | 65 |
| Percentage of palpable spleens | 100 |
| Average weight of spleen | 580 Gm |
| Percentage showing congestion in spleen | 0 |
| Percentage showing pigment in spleen | 58 |
| Percentage showing leukocytes (neutrophilic) in spleen | 72 |
| Percentage showing leukocytes (eosinophilic) in spleen | 54 |
| Percentage showing germ centers in spleen | 16 |
| Percentage showing lymph follicles in spleen | 100 |
| Percentage showing thickened blood vessels in spleen | 25 |
| Percentage showing hyalinized blood vessels in spleen | 0 |
| Percentage showing fibrocytes | 33.5 |
| Percentage showing fibroblasts | 100 |
| Percentage showing atrophic endothelocytes | 83 |
| Percentage showing normal endothelocytes | 33.5 |
| Percentage showing endothelioblasts | 33 |
| Percentage showing leukoblasts (myelocytes) | 18 |

Cirrhosis and Splenomegaly—In this condition, the enlargement of the spleen and anemia were not the chief and most obvious complaints. The patients were suffering from ascites, which was apparently secondary to hepatic cirrhosis. Whether these cases belong in the group of splenic anemias or not may be a question. This series includes fifteen such cases, and the data in table 5 may be of significance.

Splenomegaly—In this group are included those cases which were characterized by excessive splenic enlargement without severe anemia or with no anemia and no ascites. They may belong in the group of splenic anemia without the characteristic anemia or in the group of cirrhosis without ascites. If they belong to either group, they represent a stage of the disease in which the general or extrasplenic manifestations are absent. The facts observed are shown in table 6.

Gaucher's Disease—This condition, which has the clinical characteristics of splenic anemia, is differentiated from splenic anemia merely by the so-called endothelial proliferation in the splenic sinuses. In general, the spleens have the gross and microscopic appearance of those in cases of splenic anemia. If, however, the endothelial proliferation is exten-

TABLE 6—Data for Patients with Splenomegaly

| | |
|---|----------|
| Average age of patient | 43.5 yrs |
| Percentage of males | 56 |
| Percentage of palpable spleens | 100 |
| Average weight of spleen | 920 Gm |
| Percentage showing congestion in spleen | 9 |
| Percentage showing pigment in spleen | 60 |
| Percentage showing leukocytes (neutrophils) in spleen | 54.5 |
| Percentage showing leukocytes (eosinophils) in spleen | 39 |
| Percentage showing germ centers in spleen | 0 |
| Percentage showing lymph follicles in spleen | 82.5 |
| Percentage showing thickened blood vessels in spleen | 44.5 |
| Percentage showing hyalinized blood vessels in spleen | 13 |
| Percentage showing fibrocytes | 63.5 |
| Percentage showing fibroblasts | 71.5 |
| Percentage showing atrophic endotheliocytes | 68 |
| Percentage showing normal endotheliocytes | 41 |
| Percentage showing endothelioblasts | 18 |
| Percentage showing leukoblasts (myelocytes) | 13 |

sive, the cut surface of the organ presents a mottled appearance, there are darker areas which are composed of masses of the so-called Gaucher cells. The condition as seen in a few cases has been well described by Wilson⁵ and Giffin⁶ and Mayo.⁷ During the last year, Perez Fontana in his studies of connective tissue in the spleen has also included results of studies made at the Mayo Clinic on Gaucher spleens and has come to the conclusion that the typical Gaucher cell is not an endothelial cell, but that it belongs to the fibroblastic group and is therefore a part of

5 Wilson, L. B. The Pathology of Splenomegaly. A Study of the Operative and Autopsy Material from the Mayo Clinic, Surg. Gynec. Obst., 1913.

6 Giffin, H. Z. The Diagnosis of Diseases Associated with Enlargement of the Spleen, Journal-Lancet, 1913, p. 97.

7 Mayo, W. J. Surgery of the Spleen, Surg. Gynec. Obst., 1913, The Relation of the Spleen to Certain Chronic Purpuras, Surg. Gynec. Obst. 40:771 (June) 1925.

the reticulum. He maintains that the spleen has the elemental structure of the omentum and that, as in the omentum, the fibroblasts become large and are filled with lipoid material, thus forming the fat cells of that organ. From Fontana's observations which I have had occasion to study, his contention seems correct, the Gaucher cells are probably not endothelial and are usually outside of the sinuses. This is, however, probably only of academic importance and does not have any apparent bearing on a practical conception of the disease, which seems to behave like splenic anemia with a more rapidly fatal course. The specimens in this series are too few to permit any conclusions in relation to other types of splenomegaly.

Hemorrhagic Purpura—In this group are included cases characterized by "chronic recurrent types of purpura hemorrhagica with low platelet count, nonretractile clot, long bleeding time and positive tourniquet or capillary resistance test. In many cases, petechiae and ecchymoses dated from childhood. Bleeding in most cases was from the nose, gums and uterus" (Giffin⁸). Bleeding from the bowel occurs in some cases. The spleens appear normal, although slightly increased in size, they do not show anything especially characteristic in this series, and they are too few for any definite conclusions to be drawn.

SUMMARY OF ITEMS NOTED

Age—It may be seen that splenic anemia or Banti's disease is a disease which occurs during early life, appearing on the average of ten years earlier than does pernicious anemia, cirrhosis with splenomegaly or uncomplicated splenomegaly. It occurs, however, about ten years later in life than hemolytic icterus, and it appears at about the same period in life as does myelogenous leukemia.

Sex—Splenic anemia, pernicious anemia, cirrhosis with splenomegaly and uncomplicated splenomegaly are much more common in males, while myelogenous leukemia is more common in females, hemolytic icterus occurs about equally in both sexes.

Size and Weight of Spleen—The smallest spleens in this series occur on the average in patients with pernicious anemia, and therefore are less frequently palpable. In all other conditions the great size and associated weight make them palpable in practically all cases in which operation has been performed. This fact does not mean that in all conditions which belong to splenic anemia, hemolytic icterus, myelogenous leukemia, hepatic cirrhosis and uncomplicated splenomegaly, the patients have large spleens. In general, when the diagnosis is made the spleens are easily palpable, but in all probability there are stages in the diseases when the

⁸ Giffin, H. Z., and Holloway, J. K. A Review of Twenty-Eight Cases of Purpura Haemorrhagica with Splenectomy, *Am J M Soc* **170** 186, 1925.

spleens are not so large. There was a time, not more than twenty years ago, when most if not all recognizable types of carcinoma of the stomach were palpable, but at present, as observed in modern clinics, many of the types of gastric carcinoma are not palpable. It may be possible that the condition of knowledge relative to splenic conditions is in the stage in which one sees only the large spleens that are present in the late stages of the disease.

Congestion and Pigmentation—Congestion in the spleen is probably not unlike that in any other part of the body. It is an accompaniment of early active irritation, actual partial vascular obstruction or a low grade irritation without rapid production of scar tissue. As such it is more marked in youth, and when present later in life, it occurs in regions in which previous destruction has not occurred. It is most marked in hemolytic icterus and pernicious anemia, one condition occurring in early life and the other in middle life. Both diseases are accompanied by and characterized by erythrocytic pigment in the spleen, despite the fact that they do not show evidence of old chronic changes. Both diseases are relatively acute. The fact that one is usually cured by removal of the congested organ and the other is not cured by the same treatment suggests that in one the congestion may have its primary cause in the spleen, while in the other the congestion is secondary to an attempt to care for products of destruction originating elsewhere in the body. Pigmentation occurs in all of this series of spleens, but it exists only in small quantities in all but hemolytic icterus and pernicious anemia.

Neutrophilic Leukocytes—When these cells are present in great numbers in any localized area of the body, or when they are increased in the circulating blood, an acute infection is usually indicated. In none of this series of conditions was there a great increase in their number. They are present, but there is too great a similarity in their relative presence to allow speculation concerning their significance. They are least frequent in hemolytic icterus.

Eosinophilic Leukocytes—Like the neutrophilic leukocytes, they are not so common. One observation may be of significance. The pigment in all types of enlarged spleens of the series is usually found in eosinophilic leukocytes. In some of the fibrotic spleens, such as those found in patients with splenic anemia, hepatic cirrhosis and uncomplicated splenomegaly, much of the pigment is extracellular. In pernicious anemia, in which eosinophilic leukocytes are particularly common, they contain much pigment.

Lymph Follicles and Germ Centers—These are present in all spleens of the series, and their relative number and presence show little differences. In general, the figures show that the lower the average age the

more prominent is their presence. The germ centers in the fibrotic spleens are less conspicuous. The exception to this may be found in the cases of splenic anemia in which the greatest number of germ centers appear. This may be due to the fact that this disease attacks people in early life, when there is normally greater regeneration of tissues. This phenomenon of regeneration is especially visible in splenic anemia, lymphoblasts of the centers and fibroblasts of the reticulum are numerous.

Thickened Walls of Blood Vessels—The vessels especially observed in this series were those which traverse the malpighian corpuscles or lymph follicles eccentrically, since they are the small branches which are most intimate with the perifollicular reticulum and sinuses. The thickening of the wall is most marked in splenic anemia and pernicious anemia and least marked in hemolytic icterus and hepatic cirrhosis. It is found in varying degrees in all spleens in the series.

Hyalinization of the Walls of the Vessels—Closely related to fibrosis is hyalinization, since fibrosis probably always precedes hyalinization. Marked parallelism is seen between the two conditions in the different spleens. In pernicious anemia, however, hyalinization is common and occurs in a much higher percentage of spleens than in all other conditions.

Increase in Fibrocytes and Fibroblasts—In an organ which is normally not composed of great numbers of fibrocytes, their easily recognizable increase may be interpreted as a replacement of other structures which have been destroyed. The absence of fibroblasts in great numbers in the presence of great numbers of fibrocytes suggests a completed process, but when both fibrocytes and fibroblasts are present, one may perhaps rightly consider that the process of destruction and replacement is incomplete. In splenic anemia, both types of cells are abundant. This may also be said of uncomplicated splenomegaly although both fibroblasts and fibrocytes are in general less frequent than in splenic anemia. In hepatic cirrhosis the spleen does not contain fibrocytes in great abundance, but fibroblasts are in greater abundance than in any other condition. This suggests that the process of replacement in the spleen is active, and that it is not of so long a duration as in splenic anemia. The relatively small number of fibroblasts and fibrocytes in hemolytic icterus, pernicious anemia and myelogenous leukemia suggests the comparative absence of destruction of the splenic tissues in these diseases.

Atrophic Endotheliocytes of the Sinuses—There is an interesting parallelism between the increase in the fibroblasts and fibrocytes and the presence of these atrophic endotheliocytes. All three are conspicuously increased in splenic anemia, hepatic cirrhosis with splenomegaly and

uncomplicated splenomegaly, and are conspicuously infrequent in hemolytic icterus, pernicious anemia and myelogenous leukemia

Normal Endotheliocytes of the Sinuses—The sinuses in hemolytic icterus, pernicious anemia and splenic anemia show a higher percentage of apparently normal endotheliocytes. Their presence seems to be inversely proportional to the presence of increased fibrocytes, with the exception of splenic anemia in which fibroblasts and fibrocytes are greatly increased. This may be explained, perhaps, on the ground that splenic anemia is a disease of young persons and occurs rather acutely before atrophic changes have a chance to occur in the sinuses.

Endotheloblasts Lining the Sinuses—These cells are characterized by being large and containing large nuclei and nucleoli. They line the sinuses under certain conditions, being especially abundant in myelogenous leukemia. They are sometimes seen in all other conditions, but their increased presence in myelogenous leukemia suggests some possible relationship between the abnormal abundance of leukoblasts in the circulating blood and the tissues. This suspicion is greatly enhanced by virtue of the fact that many of these cells contain protoplasmic granules, although these granules are usually smaller than those seen in leukoblasts. Endotheloblasts are also common in pernicious anemia.

Leucoblasts (Myelocytes)—In the present work, distinction is not made between the neutrophilic, eosinophilic and basophilic leukoblasts. They are more common in myelogenous leukemia. They are next more frequent in pernicious anemia. There seems to be a parallelism between their presence and the abundance of endotheloblasts lining the sinuses.

In this brief report there seems to be no way of recognizing the clinical entity from the splenic condition alone except in extremes of myelogenous leukemia and in different types of splenomegaly which belong to either splenic anemia or hepatic cirrhosis. In general Gaucher's disease may be recognized by the presence of the so-called Gaucher's cells, although a few of these may be found also in splenic anemia. There is some evidence to suggest a possible relationship between some of the diseases which have been described, but further study must be made before any definite report is justifiable. The problem in the normal structure of the spleen remains unsolved for the present. This has to do with the exact method of entrance of the circulating blood into the so-called sinuses and the relation of the sinuses to the splenic veins.

ABSTRACT OF DISCUSSION

DR. WARD J. MACNEAL, New York. It is possible to recognize a definite anatomic unit of the structure of the spleen which can properly be designated as a splenic lobule, and it is easily recognized because it possesses the splenic follicle at its center. This is a new conception, I think, of the splenic unit. Second, the

arterial capillaries of the spleen terminate by opening into and becoming continuous with the intercellular spaces of the splenic pulp. This has been demonstrated in serial sections of the spleens of animals and of man and also by the experiment of injecting nucleated corpuscles of the blood of a bird into a tributary of the splenic artery so that these cells are injected into the spleen during life by arterial pressure.

DR. WILLIAM C. MACCARTY, Rochester, Minn. This winter I had the pleasure of seeing Dr. MacNeal's work. I have kept and expect to keep an open mind on the subject of the structure of the spleen and the relation of the arteries to the sinuses. I have two associates working with me now on circulation, and I am going to wait until they make their observations, compare them with Dr. MacNeal's and others and then, perhaps, draw conclusions.

THE INTRADERMAL SALT SOLUTION TEST IN TUBERCULOSIS

AARON FELDMAN, M D

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In a recent publication, Feldman and Reifsneider¹ briefly reviewed previous work with the intradermal salt solution test² and reported results of its use in a series of cases of nephritis. McClure and Aldrich,³ who introduced the test in 1923, found that the elevation produced by the injection of salt solution disappeared more quickly than normally in the presence of edema or pre-edema. They³ suggested the possibility that the rapid disappearance of the type studied in cases of edema with associated albuminuria might be due to a toxic condition of the tissues which increases their affinity for water. Results from the use of the test by Baker⁴ in scarlet fever, by Lash⁵ in toxemia of pregnancy, by Olmstead⁶ in a certain group of cardiac cases and by Harrison⁷ in pneumonia in children, tend to show a relationship between the toxicity or severity of illness of the patient and the disappearance time.

The present paper reports results obtained by the use of the intradermal salt solution test on twenty-nine patients in the tuberculosis department of the Cook County Hospital. Twenty-five of these had a

*From the Otho S. A. Sprague Memorial Institute and the Pathological Laboratory of the Cook County Hospital.

1 Feldman, Aaron, and Reifsneider, J. S. Arch Int Med, **41** 102 (Jan) 1928

2 The technic of the test is as follows. A small elevation is raised by the intracutaneous injection of 0.2 cc. of a sterile 0.8 per cent aqueous solution of sodium chloride. The length of time that the elevation remains palpable is noted. Normally, this time is at least one hour in children of more than 1 year of age, somewhat longer in white adults and still longer in negro adults. The tests reported here were performed mostly on the forearm, because, as has been pointed out by McClure and Aldrich, shortened time during which the elevation remains palpable due to deficient circulation is less frequently found here than in the leg.

3 McClure, W. B., and Aldrich, C. A. Time Required for Disappearance of Intradermally Injected Salt Solutions, J. A. M. A. **81** 293 (July 28) 1923, The Intradermal Salt Solution Test, J. A. M. A. **82** 1425 (May 3) 1924.

4 Baker, W. J. Intradermal Salt Solution Test in Scarlet Fever and Diphtheria Patients, J. A. M. A. **83** 1566 (Nov 15) 1924.

5 Lash, A. F. Intradermal Salt Solution Test in Normal and Toxaemic Pregnancies, Diagnostic and Prognostic Aid, Surg. Gynec. & Obst. **43** 40 (July) 1926.

6 Olmsted, H. C. Intradermal Salt Solution Test in Cardiac Diseases in Children. Arch Int Med **37** 281 (Feb) 1926.

7 Harrison, J. Intradermal Salt Solution Test in Lobar Pneumonia in Children, J. A. M. A. **84** 1258 (April 25) 1925.

Results of Injection of Intradermal Salt Solution List on Twenty-Nine Tuberculous Patients

| Case | Initials Race Sex Age | Diagnosis | Date of Skin Tests | Tuberculin | | Disappearance in Minutes | Comment | Clinical Notes |
|------|--------------------------------|--|--------------------------|------------|------|-----------------------------|---|---|
| | | | | 1 mg | 1 mg | | | |
| 1 | (G B) Colored Male 50 | Far advanced pulmonary tuberculosis, chronic emphysema | 2/23/27 2/21/27 | — | — | 111 > 60 | Very sick, dyspneic, anemic, cold | Had been sick presumably only about 1 week before admission to hospital. While in the hospital, pulse rate varied from 98 to 100, temperature from 96.2 to 97.6 and was persistently subnormal. Respirations remained at 10. Patient died 2/25/27, after 1 day in hospital. |
| 2 | (J T) Colored Male 36 | Pulmonary tuberculosis | 3/11/27 | — | — | 95 | Patient dyspneic, unconscious, anemic, moist and cold | Had pneumonia about 2 months before admission to the tuberculosis hospital, cough, weakness and expectoration for 3 weeks, loss of weight of 20 pounds (9.0 kg) in 3 weeks. Urinalysis negative. Tubercle bacilli in sputum. Roentgen-ray observations revealed fluid present in field of lower left lung in peripheral position. Patient died 3/11/27, after 6 weeks in hospital. |
| 3 | (J T) Colored Male 16 | Ulcerous pulmonary tuberculosis | 12/21/26 | — | — | 70 | | Had been sick presumably only about 3 months before admission to the hospital. Pulse rate varied from 81 to 128, respirations, 20 to 22, temperature, 97.6 to 101.1 F. Had an afternoon elevation of temperature regularly. He was well developed and muscular but looked entirely ill. No tubercle bacilli found in sputum. Roentgen-ray observations: ulcerous pulmonary tuberculosis involving both upper lobes, with a large cavity in left upper lobe near vertebral column. Patient died 1/7/27, after 5 weeks in hospital. |
| 4 | (J R) Colored Male 11 | Pulmonary tuberculosis | 12/23/26 | — | — | 70 | | Necropsy observations: extensive ulcerative and caseous bronchopneumonic tuberculosis of both lungs. Was considered to have a mild, doubtful case, but later became worse. Did not seem acutely ill at the time of the test and was allowed to walk around the ward at that time. Pulse rate varied from 60 to 72, respirations, 22 to 30, temperature, 97 to 102. Urine, negative. Tubercle bacilli in sputum. Roentgen-ray observations: ulcerous pulmonary tuberculosis involving the upper two thirds of left and upper one half of right lung. Patient died on 1/1/27, after 5 1/2 months in the hospital. |
| 5 | (G A) Colored Male 40 | Far advanced pulmonary tuberculosis | 3/11/27 | — | — | 60 | Potentially cold | Contracted a cold about 1 year before admission. Since then weakness and loss of weight of 25 pounds (11.3 kg). Had cough for a few months. Irregular temperature up to 3/12/27, and after that a constantly subnormal temperature. Pulse comparatively high. Patient died 3/11/27 after almost 2 months in the hospital. Cough and night sweats for 1 month prior to admission. Anemia and general weakness. Loss of weight of 10 pounds (4.5 kg) in 1 month. No hemoptysis. Slight cervical adenopathy bilaterally. Urinalysis negative. Tubercle bacilli in sputum. Roentgen-ray observations: an irregular mottling in both sides of chest, an increase in hilar shadows believed to be of tuberculous origin. Small multiple cavities appeared to be present on right side. Patient died 6/5/27, after 5 1/2 months in the hospital. |
| 6 | (P O) Mexican Male 33 | Pulmonary tuberculosis | 3/18/27 | — | — | 50 to 55 | | |

| | | | | | | | |
|----|------------------------------------|--|--|-----------------------|----------------------------|---|---|
| 7 | (C W) Colored Male 39 | Far advanced pulmonary tuberculosis | 1/27 1/28/27 | — — | 15 19 | Patient at ease, not having a high temperature in last 3 days | Presumably well until 1 month before admission, when he contracted a cold with cough and expectoration. Pulse rate varied from 78 to 124, respirations, 24 to 36. The temperature was subnormal most of the time. No tubercle bacilli found in sputum. Roentgen ray observations density increased with slight trabeculated appearance from right apex to fifth rib. Was considered as having an arrested case on discharge on 1/7/27, after 5 weeks in the hospital. |
| 8 | (H C) Colored Male 57 | Far advanced pulmonary tuberculosis, calc. arteriosclerosis, myocarditis, ancient tight sided hemiplegia, syphilis | 2/18/27 | — | 15 | — | Contracted a cold last October and gradually lost weight, 15 pounds (68 kg) since then. Expectoration for 5 years and 1 paralytic stroke 5 years ago. Had had a positive Wassermann reaction and anti-syphilitic treatment. Skin was scaling. Urinalysis negative. No tubercle bacilli found in sputum. Roentgen ray observations pleural fibrosis and fluid extending from the right second rib to the diaphragm, obliterating right lateral border. Four small cavities present in right supraclavicular region, not accompanied, however, by tuberculous mottling. Was not considered as having a far advanced case at the time of the skin tests. Patient died 5/23/27, after 3 months in the hospital. |
| 9 | (S N) Porto Rican Male 33 | Far advanced pulmonary tuberculosis and nodular, gastro intestinal tuberculosis | 1/27/27 2/3/27 | — | 35 25 | Patient in serious condition | Had had recent hemorrhages when tested. Tubercle bacilli in sputum. Patient died 1/3/27, after 7 months in the hospital. |
| 10 | (J B) White Male 44 | Far advanced pulmonary tuberculosis | 2/19/27 2/21/27 | — | 30 38 | — | Presumably sick for only 2 months prior to admission. Urinalysis negative. No tubercle bacilli found in sputum. Patient died 2/23/27, after 3 weeks in the hospital. |
| 11 | (W L) Colored Male 28 | Far advanced bilateral ulcerative pulmonary tuberculosis | 1/10/27 1/12/27 | — | 31 30 | Irritation of, renal genital involvement? | Stated that he had been well up to 3 to 4 weeks before admission. Pulse rate went up to 144, respirations to 40 and the temperature to 104. Urinalysis albumin, positive, sugar, negative. No tubercle bacilli found in sputum. Patient died 1/11/27, after 11 days in the hospital. |
| 12 | (F R) Colored Male 20 | Far advanced pulmonary tuberculosis | 1/6/27 1/7/27 1/8/27 1/11/27 1/15/27 | — — — — — | 30 27 30 30 25 | Left leg swollen Unable to talk | On admission complained of cough, 1 month, weakness, 2 months, loss of weight of 15 to 20 pounds (68 to 90 kg) in 2 months, and night sweats, 2 months. Was acutely ill, greatly emaciated and very weak. Physical observations were those of advanced tuberculosis. Temperature varied from 98 to 101.6 F., pulse rate from 88 to 144, respirations from 26 to 48. Urinalysis albumin, positive, sugar, negative. No tubercle bacilli found in sputum. Patient died 1/16/27, after 2 weeks in the hospital. |

> == more than, ± == about, + == present, — == absent

Results of Injection of Intradermal Salt Solution Test on Twenty-Nine Tuberculous Patients—Continued

| Case | Initials Race Sex Age | Diagnosis | Date of Skin Tests | Idema | | Disappearance Time in Minutes | Comment | Clinical Notes |
|------|----------------------------------|---|--|------------------|------------------|-------------------------------------|---|---|
| | | | | Arms | Legs | | | |
| 13 | (D. B.) Colored Male 33 | Moderately advanced pulmonary tubercu- losis with far advanced genito urinary tuberculosis | 12/26/26 | — | — | 28 to 30 | | Had one tuberculous testicle removed about 3 to 4 years ago. Many discharging sinuses with extravasation of urine in the lower part of the abdomen. Urinalysis albumin, positive; blood, positive tubercle bacilli in sputum. Typical history and observations of pulmonary tuberculosis. Had a persistently low temperature in the last 8 days of life. Patient died on 1/8/27, after 7 weeks in the hospital. |
| 14 | (T. M.) White Male 29 | Far advanced pulmo- nary tuberculosis | 3/ 5/27 | — | — | 25 to 30 | | History very much like that in gastric ulcer. On roentgen ray examination pulmonary tuberculosis was discovered and was con- firmed by sputum examination. Considerable emaciation and a high temperature from time to time. Urinalysis negative. Roent- gen ray observations on 1/3/27, ulcerous pulmonary tubercu- losis with multiple cavity formation involving both upper lobes. Patient died 3/7/27, after 5 weeks in the tuberculosis hospital. |
| 15 | (G. W.) White Male 38 | Far advanced pulmo- nary tuberculosis | 1/ 7/27 1/ 8/27 1/ 9/27 1/13/27 | — — — — | — — — — | 20 30 15 23 | Somewhat yellow, lips, gums, and con- junctiva very pale. Looks very pale. | Caught a "cold" last July in a hospital. On admission had had a cough for 3 months, loss of weight of 10 pounds (181 kg.) in 3 months, pain in the chest, and hemoptysis for 1 month. Tem- perature varied from 98 to 102 F., pulse rate from 92 to 116, res- pirations from 21 to 36. Urinalysis negative. No tubercle bacilli found in sputum. The disease evidently took a very rapid turn for the worse in the last few days of life. Patient died 1/16/27, after 13 days in the hospital. |
| 16 | (I. L.) Colored Male 28 | Far advanced pulmo- nary tuberculosis, emphysema, draining peltonitis | 2/23/27 2/24/27 2/26/27 | — — — | — — — | 25 25 15 | | On admission, had fluid in abdomen and was acutely ill. Tempera- ture varied from normal to 101 F., pulse rate from 92 to 128, respirations from 20 to 40. Urinalysis negative. Blood chemistry total nonprotein nitrogen, 18 mg., creatinine, 1.9 mg., uric acid, 27 mg., sodium chloride, 0.52 per cent, cholesterol, 0.18 per cent on 2/1/27. No tubercle bacilli found in sputum. Patient died 2/28/27, after 5 weeks in the hospital. |
| 17 | (I. L.) Colored Male 23 | Far advanced pulmo- nary tuberculosis, emphysema, draining sinuses in left lower axillary space | 12/23/26 1/10/27 1/20/27 | — — — | — — + | 18 to 20 23 33 | No elevation of afternoon tem- perature | A rather thin colored man with a history of emphysema of 8 months' duration. During January developed edema, first of the right leg, then of the left leg and the serotum, it became generalized in the last few days of life. Tubercle bacilli in sputum. Patient died 2/21/27. |
| 18 | (J. D.) White Male 39 | Far advanced pulmo- nary tuberculosis, alcoholism | 1/13/27 1/14/27 1/15/27 | — — — | — — — | 20 20 25 | | An emaciated, acutely ill person. History of tuberculosis for 8 years and chronic alcoholism. Urinalysis negative. Blood chem- istry total nonprotein nitrogen, 30 mg., uric acid, 2 mg., sodium chloride, 0.15 per cent, carbon dioxide capacity, 19 on 1/13/27. No tubercle bacilli found in sputum. Patient died 1/19/27, after 2 weeks in the hospital. |

| | | | | | | |
|----|--------------------------------------|--|--|-----------------------|--|---|
| 19 | (L K) Colored Male 23 | Far advanced pulmonary tuberculosis of 4-5 | 1/19/27 1/20/27 | — — | 20 14 | Contracted a cold about 4 months before admission. Typical history and observations of pulmonary tuberculosis with a high temperature and pulse rate most of the time. Urinalysis negative. No tubercle bacilli found in sputum. Patient died 2/4/27, after 3 weeks in the hospital. |
| 20 | (W M) Colored Male 71 | Far advanced pulmonary tuberculosis with cavitation | 1/21/27 1/21/27 2/2/27 2/3/27 2/4/27 | — — — — — | 20 to 25 15 20— 15— 20 to 22 | Knowledge of tuberculosis for 3 years and cough and expectoration for 3 months. Greatly emaciated with quite regular in afternoon elevation of temperature as high as 102.2. Pulse rate rapid most of the time, as high as 142. Respirations from 22 to 32. Blood chemistry: total non-protein nitrogen, 23 mg.; creatinine, 14 mg.; uric acid, 21 mg.; sodium chloride, 0.48 per cent; cholesterol, 0.125 per cent; carbon dioxide capacity, 51.02. 1/21/27. No tubercle bacilli found in sputum. Patient died 2/7/27, after 22 weeks in the hospital. |
| 21 | (L L) Colored Male 29 | Far advanced pulmonary tuberculosis | 1/10/27 1/11/27 1/12/27 | — — — | 14 15 13 | History of cough of from 9 to 10 months duration and 1 month twice in the last 8 months. Clinical history and physical observations of tuberculosis. Urinalysis negative. Tubercle bacilli found in sputum. Patient died 1/12/27, after 2 weeks in the hospital. |
| 22 | (Y P) Colored Male 19 | Far advanced bilateral pulmonary tuberculosis | 2/23/27 2/24/27 2/25/27 | — — — | 17 15 10 | Sick only 4 months when he entered the hospital. Had lost about 50 pounds (227 kg.) and had been hoarse for about 2 weeks. Pulse rate varied from 100 to 134. Respirations from 22 to 24. Temperature from 99.6 to 101.3 F. Was acutely ill. No tubercle bacilli found in sputum. Patient died 2/26/27, after 6 days in the hospital. |
| 23 | (L F) White Female About 40 | Far advanced pulmonary tuberculosis | 1/17/27 | — | 12 | An emaciated white woman with thin arms. History of a cold of 12 years' duration and sore throat and aphonia for 3 weeks. Tubercle bacilli in sputum. Patient died 1/15/27, after 4 days in the hospital. |
| 24 | (B D) Colored Male 24 | Far advanced pulmonary tuberculosis with draining appendiceal scar sinus | 1/19/27 1/20/27 | — — | 10 21 | An emaciated man with a peeling skin and very little subcutaneous fat. Presumably well up to August 1929, when he had an appendectomy. Urinalysis negative. Tubercle bacilli in sputum. Patient died 1/26/27, after 8 days in the hospital. |
| 25 | (A M) White Male 15 | Miliary tuberculosis, acute disseminated tuberculosis, tuberculosis of second lumbar spine | 12/28/26 | — | 20 | History of a previous injury to the spine. A thin emaciated white boy, who looked cyanotic and acutely ill but was rational. Roentgen ray observations: tuberculous spondylitis, miliary tuberculosis of both lungs. Died 12/27/26, after a month in the hospital. |

> = more than, ± = about — = present, — = absent

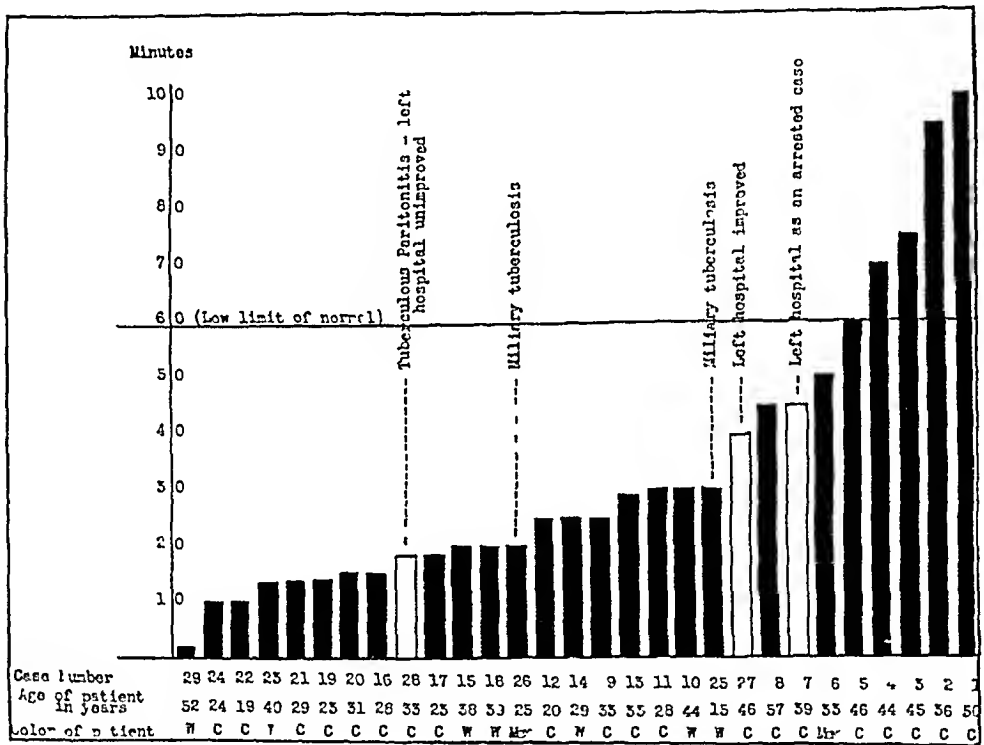
Results of Injection of Intracuticular Salt Solution Test on Twenty-Nine Tuberculous Patients—Continued

| Initials Race Sex Age | Diagnosis | Date of Skin Tests | Prima Arms Legs | Disappear in Minutes | Comment |
|--------------------------------------|--|--|-----------------------|--|--|
| 26 (J G.) Mexican Male 25 | Miliary tuberculosis | 2/ 2/27 2/ 3/27 2/ 1/27 | — — — | 20 23 20 | Well until 1/13/27 On admission complained of cough, fever, anorexia, hoarseness Was dyspneic Roentgen ray observations flecked markings throughout lung fields, presumably miliary tuberculosis Wassermann test negative White blood cells, 3,200 (1/23/27) White blood cells, 4,100, polymorphonuclears, 70 per cent, lymphocytes, 21 per cent (1/30/27) Blood chemistry total nonprotein nitrogen, 33.3 mg, urea nitrogen, 16 mg, ure acid, 1.8 mg, sodium chloride, 6.30 per cent, cholesterol, 0.125 per cent, carbon dioxide capacity, 57 (2/1/27) Widal test negative No tubercle bacilli found in sputum Died 2/7/27 after 2 weeks in the hospital |
| 27 (F K.) Colored Female 46 | Bilateral pulmonary tuberculosis, tuberculous peritonitis | 11/30/26 | — — — | 30 | History of abdominal pain and swelling for 7 months, cough, 3 weeks, and marked loss of weight In past history, moderate alcoholism and probable syphilis Had chest symptoms which suggested tuberculosis, and a distended abdomen Septic afternoon temperature in the first two weeks Much improved on discharge, 12/28/26, after 5 weeks in the hospital, having had normal temperature for several days Urine negative Blood pressure 110/60 Wassermann test plus Blood chemistry normal No tubercle bacilli found in sputum |
| 28 (I H.) Colored Male 33 | Tuberculous peritonitis | 12/ 7/26 12/10/26 12/14/26 12/15/26 12/16/26 12/18/26 | — — — | 40 30 18 18 to 20 18 20 to 25 | History of pain and swelling of abdomen, 3 weeks, chills, fever and sweats, 5 weeks, and considerable loss of weight The observations were distended abdomen, liver and spleen not palpable following an abdominal paracentesis in which 3,000 cc of fluid of specific gravity 1.020 were removed Had septic afternoon temperature, with rapid pulse and respiration Urinalysis albumin, trace, sugar, negative, pus cells, positive, granular casts, few Blood pressure, 100/60, hemoglobin, 80 per cent, red blood cells, 4,700,000, white blood cells, 4,650 Smear of paracentesis fluid showed a pre dominance of lymphocytes Was discharged with condition unchanged 12/29/26, after 1 week in the hospital |
| 29 (I R.) White Male 52 | Chronic ulcerative tuberculosis of right apex with cavity, hypostatic pneumonia with effusions of liver and generalized miliary tuberculosis | 11/16/26 11/17/26 | — — — | 2 to 3 1 | On admission looked cyanotic, drowsy, and was holding eyes as if moribund History of loss of 30 pounds (13.6 kg) in weight, weakness and gastrointestinal distress in the last 1 month, swelling of abdomen in the last 2 months Past history chancres 20 years ago, gonorrhea several times, epilepsy and alcoholism Observations: dullness in lungs, swollen abdomen, edema of ankles and lower part of legs, greatly emaciated arms Urinalysis negative Blood chemistry negative Blood pressure 98/80 Wassermann negative Tubercle bacilli in sputum Died 11/18/26, after 5 days in the hospital Necropsy observations: generalized miliary tuberculosis of lungs, liver, spleen, kidneys, and mesenteric and abdominal lymph glands Extreme ulceraceous tuberculosis of lungs, ileum and urinary bladder, atrophic cirrhosis of liver, hydrothorax, hydropertoneum |

> = more than ± = about, + = present — = absent

condition diagnosed as pulmonary tuberculosis, two had miliary tuberculosis, one, an acute miliary tuberculosis terminating in ulcerative pulmonary tuberculosis, and one, tuberculous peritonitis. All except three died while in the hospital, two were discharged improved and one unimproved. Edema was not palpable in the arm in any case, it was found in only three cases in the leg. The results of the tests and the clinical data are given in the table and are shown in the chart which was constructed from data taken from the table.

It is seen that in this group of patients with advanced tuberculosis, the disappearance time is usually markedly low. In sixteen patients, the time was only twenty-five minutes or less, most of them showed symp-



The heights of the columns represent the variations in the shortest time required for elevations caused by the injection of salt solution into the forearm to disappear in twenty-nine cases of tuberculosis. The black columns represent the patients who died in the hospital and the white columns those who were discharged. W indicates the white patients, C, the colored, and Mex, the Mexican.

toms of being toxic, some were irrational. One was a young Mexican man with a typical clinical and roentgen-ray picture of miliary tuberculosis. Although most of these patients showed a marked rise in temperature, pulse and respiration rate, a close relationship between these factors and the short disappearance time was not evident. Edema did not occur in the arms in any of these patients, in only two (cases 12 and 28) was there evidence pointing to involvement of the urinary

tract Many of these patients were greatly emaciated, which naturally suggested that this loss of tissue might perhaps account for the short disappearance time. However, this explanation seems to be inadequate, since the disappearance time was long in some greatly emaciated individuals.

The results did not vary a great deal in the few patients on whom the tests were carried out both in the forearm and in the leg.

That tuberculosis does not necessarily lead to a low disappearance time can be readily seen from the chart. Of the eight patients that showed a disappearance time of forty-five minutes or more, three (cases 4, 6 and 7) were considered to have mild cases at the time of the tests, two of them died several months later. Two patients (cases 3 and 8), although seriously ill at the time of the tests, were not considered as having far advanced cases, one of these, however, died two weeks later. The remaining three (cases 1, 2 and 5) had only a few more days to live, although they gave histories of short duration of illness. It is worthy of note that these three patients with the longest disappearance times seemed to show little temperature reaction. The one who had the highest disappearance time in the entire series (one hour and fifty minutes) had a persistently subnormal temperature ranging between 96.2 F and 97.6 F. In these three patients, the forearms were observed to be cold when exposed for a short time. All were greatly emaciated, which tends to show that emaciation alone is not sufficient to explain the low results obtained in the larger number of cases, furthermore, the young Mexican with a typical picture of miliary tuberculosis and a disappearance time of twenty minutes was not emaciated.

The remaining five patients in different states of the disease gave results varying from twenty-eight to forty minutes.

Since most of the patients tested were negroes the low results are of enhanced significance, because the normal disappearance time has been shown Lash⁵ to be considerably higher in negro women than in white women.

SUMMARY

The intradermal salt solution test was performed on twenty-six patients with pulmonary tuberculosis, two with miliary tuberculosis, one with pulmonary and acute miliary tuberculosis, and one with tuberculous peritonitis. In twenty-four of the twenty-nine patients the disappearance time of the elevation caused by the injection fell below the lower limit of normal, and in most of these it was greatly below normal.

In general, the shortest times were obtained in patients with symptoms of toxicity, who in many instances had a septic type of temperature. Extended disappearance time was usually noted in patients with a tendency to subnormal temperature.

That pulmonary tuberculosis does not always cause a markedly short disappearance time is shown by the observation of a disappearance time of sixty minutes or more in five patients, four of whom died within fifteen days after the time of the tests

The possibility that secondary infection may have played an important part in causing the short disappearance times in these tuberculous patients must be considered

COUNCILMANIA TENUIS AND C DISSIMILIS, INTESTINAL AMEBAS OF MAN

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The detection of distinguishing structural features that may be relied on to separate the species of amebas, especially of the parasitic amebas in the digestive tract of mammals, is fraught with difficulties. These arise from changes in form in the motile phases due to locomotion, to the extrusion and retraction of pseudopodia, to the presence of cytoplasmic inclusions and to the modifications incident on changes in temperature and in hydrogen ion concentration. For example, a slight increase in acidity, as from p_H 7.0 to 5.8, markedly increases the locomotor activity and tends to elongate the pseudopodia.

In stained preparations of motile stages, the form of the body and of the pseudopodia is subject to changes due to contraction in smearing and fixation.

In the encysted stages many of these modifications are eliminated but others arise which disturb the uniformity of structure. Among these are the volume, number, distribution and time of occurrence of the glycogen vacuoles that determine the appearance of the cytoplasm, modify the location of nuclei and determine the numbers and location of the chromatoidals.

A second cytoplasmic constituent is the chromatoidal substance organized in characteristic chromatoidal bodies that appear on the periphery of the glycogen vacuoles as the latter fade out, in the form of siderophil bodies which in turn decrease in number and finally fade out entirely with increase in the number of nuclei and aging of the cyst. These bodies have a characteristic range in size, shape and relative number in the different species of amebas. They vary greatly, however, within the species in these particulars, both with age and in different infections, probably as a result of either environmental influences or genetic or racial differences. There are stools and hosts in which chromatoidal-rich or chromatoidal-poor cysts are found that have a different appearance from each other because of the differences in the total and relative masses of chromatoidal substance and number of chromatoidal bodies. The form of these chromatoidal bodies is sometimes suggestive of liquid crystals with evidence of angular or semi-angular facets. These structural features of the chromatoidals change with their increase in size, their coalescence and their solution and fading out. Although varying greatly in size, shape and proportions, they nevertheless exhibit similarities within the species which are somewhat characteristic.

The nuclei also vary in shape, structure, number, size and location, as mitosis proceeds and the increase from 1 to 2, 4, 8, or 16 as nuclear divisions end and the cyst comes to a state of nuclear equilibrium. The number of divisions is, in the main, characteristic for each species. Thus in *Iodamoeba butschlii* the completed number of nuclei in the cyst is rarely more than one, in *Endamoeba dysenteriae*, it is never more than four, in *Councilmaniana laffleurii* and *Endamoeba coli*, it is eight or sixteen, rarely thirty-two in the former. In *C. muris* and *C. decumanus*, the maximum number is eight.

During the mitotic process the nuclei go through a succession of orderly changes in size and shape. The single nucleus of the cyst when first formed is much larger than those of the terminal stage. As each nucleus goes through mitosis, it first elongates into a broad spindle-shaped body, then constricts equatorially and greatly elongates, it parts in the middle, and each end reshapes itself into a sphere, with profound changes in internal structure during this process.

The number of the chromosomes is a characteristic of plants and animals, including amebas. The numbers and sizes of the chromosomes are basic, together with the siderophil substance forming the centrosomes at the apexes of the spindle, in determining the structure and appearance of the nucleus, not only at mitosis, but in the resting stage. The nucleus in the so-called resting stage of amebas in general thus comes to be one of the most reliable of all characters utilizable as a basis for classification and for diagnosis of species in intestinal infections. The number of chromosomes is to be detected only at, or near, the metaphase of mitosis, it is detected in relatively few infected stools, and requires skill and infinite patience to unravel, but is of greatest classificatory value in conjunction with other characteristics. Thus an ameba having about twenty chromosomes such as *Karyamoebina falcata* can not possibly be the same species as *Endamoeba dysenteriae* with only six chromosomes, as Wenyon¹ suggested.

For routine diagnosis and as a rule in specific determinations of the intestinal amebic fauna, one must make a great deal of use of the structure of the nuclei in the cysts, but nuclei utilized for this purpose are best studied when in a state of equilibrium with the mitotic divisions completed and metabolism in the cell, such as that involved in the glycogen-chromatoidal cycle eliminated or at a low ebb. In such completed cysts the maximum degree of uniformity of structure may be expected. There is even some variation in the total amount of chromatin, so that some "races" or cysts from some stools or hosts are much poorer in chromatin than others. Even with such differences, the

¹ Wenyon C. M. Protozoology. A Manual for Medical Men Veterinarian Zoologists. London: Baillière Tindall and Co., 1926, p. 209.

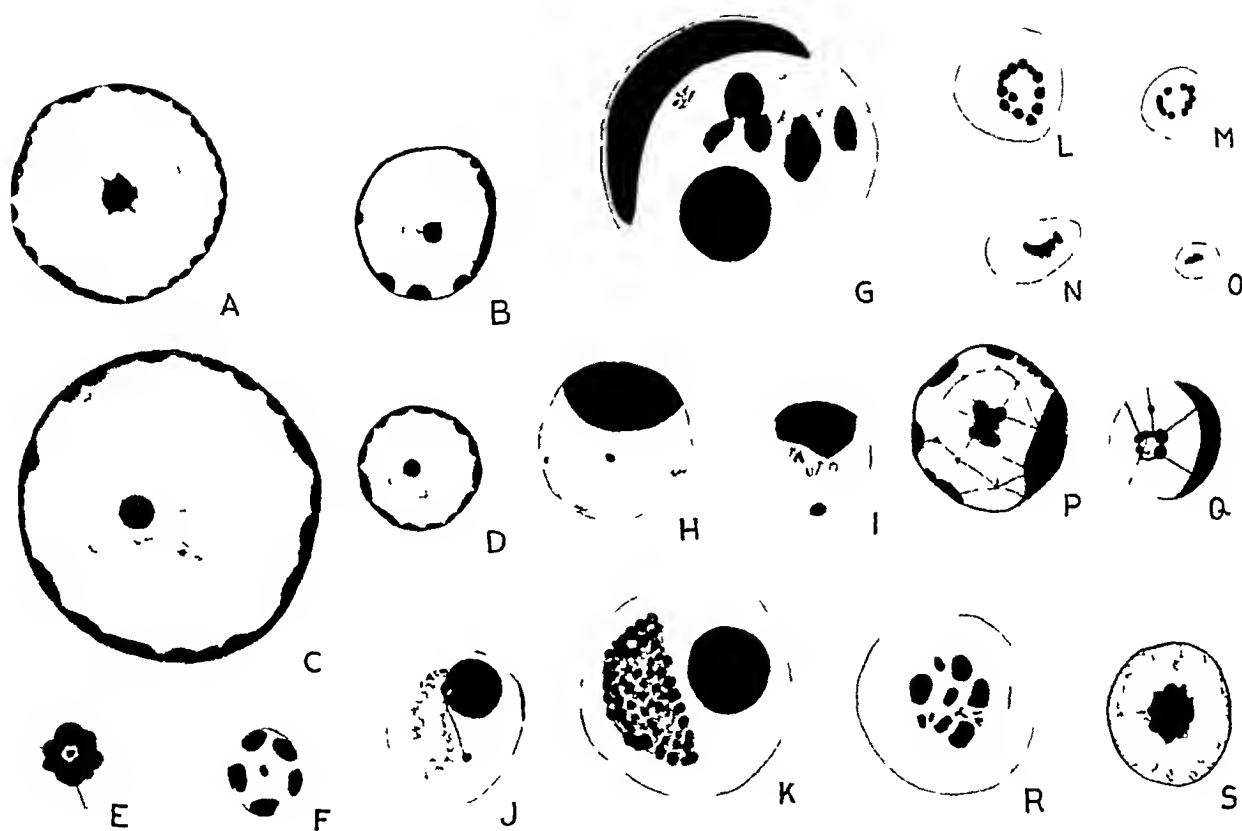


Fig 1—Comparative view of the nuclei of human intestinal amebae from fecal smears fixed in Schaudinn's fluid and stained in iron hematoxylin, $\times 4667$

EXPLANATION OF FIGURE 1

A, *Endamoeba dysenteriae* (Councilman and Laffeur) from a motile ameba in dysenteric stool, showing distributed peripheral chromatin, spoke radii, wide clear halo, and central, solid, spherical karyosome

B, *Endamoeba dysenteriae* from a four-nucleated cyst, showing smaller size but similar structure, except that the karyosome is somewhat eccentric

C, *Endamoeba coli* (Loesch) from a mononucleated cyst, showing distributed peripheral chromatin, spoke radii, small halo, and slightly eccentric, solid, spherical karyosome

D, *Endamoeba coli* from an eight-nucleated cyst, showing similar structure

E, *Dientamoeba fragilis* (Jepps and Dobell) from motile phase, showing no peripheral chromatin, nuclear membrane taint, large granules massed in large central karyosome and spoke radii to membrane

F, *Dientamoeba fragilis* showing karyosome granules scattered toward periphery

G, *Karyamoebina talcata* (Kofoid and Swezy) from a motile phase showing nuclear membrane free from peripheral chromatin except for one large crescentic blob, one large, solid, eccentric, spherical karyosome in clear halo, and some scattered chromatin blocks. Spoke radii are not present

H, *Endolimax nana* (Wenyon and O'Connor) Brug, from a mononucleated cyst showing very faint nuclear membranes, one massive, lateral, lenticular blob of chromatin, minute centrosome on stalk which is the forming intradescumose, no spoke radii, and no halo

I, *Endolimax nana* from a smaller mononucleated cyst showing intradescumose more extended, chromosomes forming in a crescent adjacent to the blob and movement of blob along intradescumose

J, *Iodamoeba butschlii* (Prowazek) Dobell from a mononucleated cyst showing taint nuclear membrane with no film of peripheral chromatin, a massive, lenticular, lateral blob and small centrosomes on stalk (the intradescumose) from blob, no halo and no spoke radii

K, *Iodamoeba butschlii* from another mononucleated cyst showing similar structure except that the crescentic mass of chromatin granules is more in evidence. This is the chromatin net from which the chromosomes will form

L, *Councilmania tenuis* (Kuenen and Swellengrebel) Kofoid from a mononucleated cyst showing deformation of nuclear membrane, lack of peripheral chromatin and central karyosome dispersed in a ring-shaped group of large granules, no spoke radii nor halo

M, *Councilmania tenuis* from a four-nucleated cyst with spherical nucleus and similar structure

N, *Councilmania tenuis* from a four-nucleated cyst with karyosome granules massed in a central crescentic mass

O, *Councilmania tenuis* from an eight-nucleated cyst with deformed nuclear membrane and minute granules massed in an elongated central karyosome

P, *Councilmania dissimilis* sp. nov. from a motile ameba in culture showing scattered peripheral chromatin and large crescentic lateral blob (oblique to plane of focus), central karyosome composed of a group of discrete granules, spoke radii and an intermediate zone of granules

Q, *Councilmania dissimilis* from an eight-nucleated cyst showing lateral blob, dispersed central karyosome and spoke radii

R, *Councilmania laffeurii* (Kofoid and Swezy) from an eight-nucleated cyst showing faint nuclear membrane with no peripheral chromatin and dispersed granules of the central karyosome

S, *Councilmania laffeurii* from a different eight-nucleated cyst with small amount of faintly stained peripheral chromatin, spoke radii, and central spheroidal mass of discrete granules forming the karyosome

microscopist may train himself to detect with a high degree of accuracy the specific distinctions between the cysts of the various amebas of the digestive tract of man

The structure of the resting nucleus in mature cysts is thus the most available and at the same time the most critical morphologic criterion of the generic and specific distinctions among the intestinal amebas of man and other mammals

It was on this basis of the structure of the resting nucleus that Kofoed and Swezy,² in part, distinguished the genus *Councilmania*, parasitica, in man. Later the species in rodents were assigned to it by Kessel³ and Kofoed, Swezy and Kessel.⁴ The striking differences in this nuclear structure as seen in the resting nucleus of the mature cysts of the different species of human intestinal amebas is shown in figure 1

In the course of our investigation on the human intestinal *Protozoa* during the past years, we have become increasingly certain that there are two additional parasitic intestinal amebas of rather frequent occurrence in man, which are at present masquerading under the cover of other better known species. Both have distinct morphologic characteristics, and infections caused by them have typical pictures of occurrence, recurrence and distribution

The first of these was originally described by Kuenen and Swellengrebel⁵ as *Entamoeba tenuis* from man. According to them, its cysts are sometimes asymmetrical, and the nuclear membranes in the cysts are devoid of peripheral chromatin in distinct blobs, although the line representing this membrane is drawn by them as a heavy one. The nuclei are characteristically deformed, off the sphere, in all of their figures. The chromatoids are rather small, rounded or rodlike. Cysts with one, two and four nuclei are figured. The nucleus has a halo and rather irregularly shaped subcentral or central karyosome.

We have long recognized this ameba in our routine laboratory examinations of stools, noting it on our laboratory records as "little *Councilmania*," but not reporting it, as we were uncertain of its status. It stains faintly, is easily confused, because of its size, and its ellipsoidal

2 Kofoed, C. A., and Swezy, O. On the Free, Encysted and Budding Stages of *Councilmania laffleurii*, a Parasitic Amoeba of the Human Intestine, Univ. Calif. Pub. Zool. **20** 169, 1923

3 Kessel, J. F. The Distinguishing Characteristics of the Parasitic Amoebae of Culture Rats and Mice, Univ. Calif. Pub. Zool. **20** 489, 1924

4 Kofoed, C. A., Swezy, O., and Kessel, J. F. On the Genus *Councilmania*, Budding Intestinal Amoebae Parasitic in Man and Rodents, Univ. Calif. Pub. Zool. **20** 431, 1923

5 Kuenen, W. A., and Swellengrebel, N. H. Korte beschrijving van enkele minder bekende protozoen uit den menschlijken darm, Nederl. Tijdschr. v. Geneesk. **57** 496, 1917

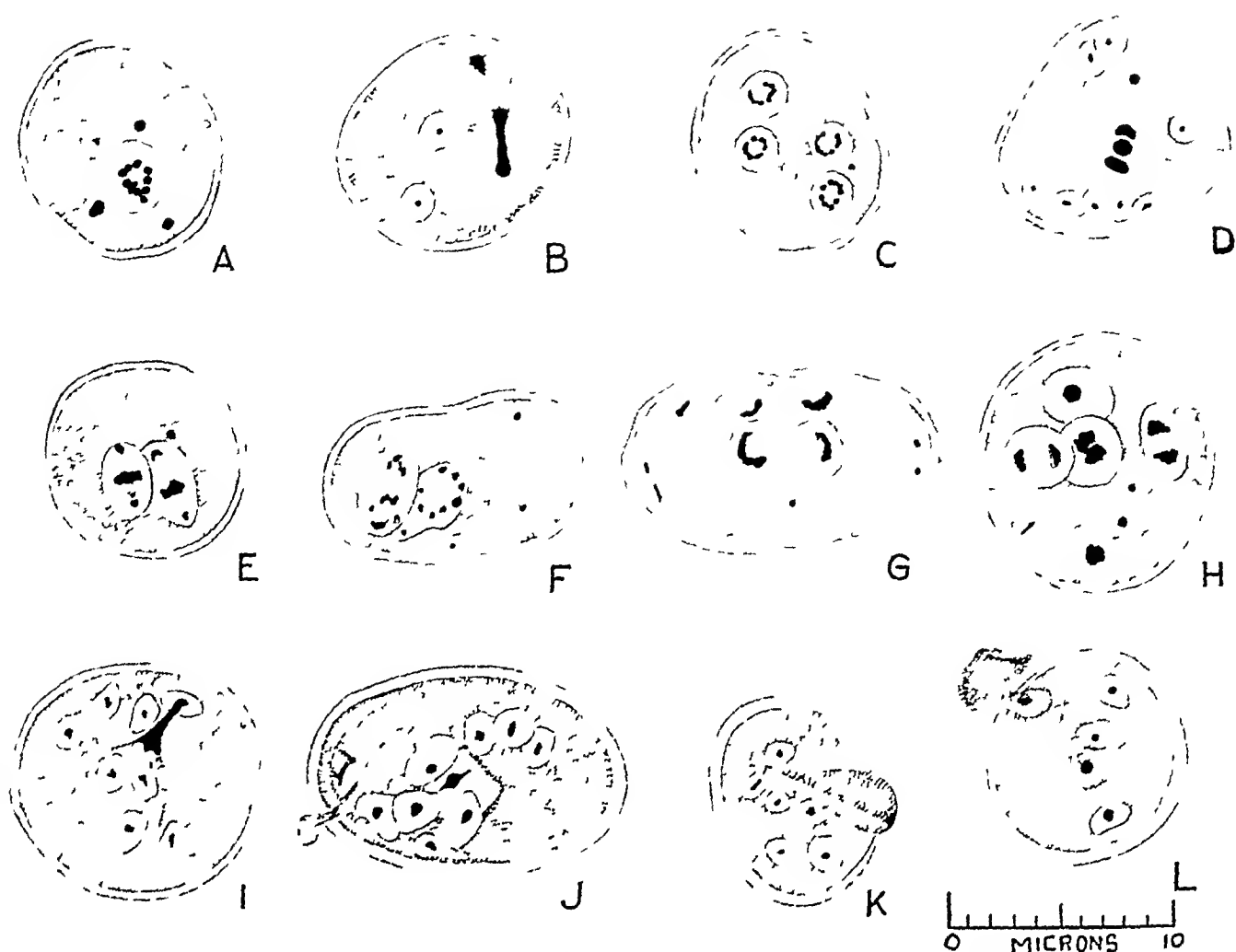


Fig 2—*Councilmama tenuis* (Kuenen and Swellengrebel) from a stained fecal smear from man from nine different cases, $\times 2,500$

A, mononucleated cyst with diffuse glycogen vacuoles, three subspheroidal chromatoids in halo, subspherical nucleus with faint membrane, no peripheral chromatin and dispersed karyosome, probably a prophase

B, binucleated cyst with diffuse glycogen vacuoles, two chromatoids, one rod-shaped in halo, and nuclei with condensed karyosomes

C, four-nucleated cyst, little evidence of glycogen vacuoles, one small chromatoid, and nuclei with dispersed ring-shaped karyosomes

D, eight-nucleated cyst with three chromatoids in one halo, and remnants of a glycogen vacuole but quite asymmetrical karyosomes

E, binucleated cyst with nuclei at metaphase of mitosis, diffuse glycogen vacuoles, and one chromatoid

F, binucleated cyst with little evidence of glycogen vacuoles, three small remnants of chromatoids and nuclei in early anaphase with about six chromosomes

G, four-nucleated cyst with little evidence of glycogen vacuoles, scattered chromatoid remnants and nuclei with crescentic karyosomes

H, four-nucleated cyst with little evidence of glycogen vacuoles, five chromatoids and nuclei all in the anaphase with chromosomes massed at the poles of the intranuclear spindles

I, eight-nucleated cyst with deformed nuclear membranes, irregular karyosomes, and several large glycogen vacuoles. Faint chromophil strands lead to the pore on the upper side from which the chromophil bud emerges

J, eight-nucleated cyst with deformed nuclear membranes, and irregular karyosomes. The remnant of a chromatoid lies in the center of a dark-bordered halo. A small cytoplasmic bud is emerging from the pore

K, six-nucleated cyst with cytoplasm emerging from pore. Probably one ameba has already escaped

L, five-nucleated cyst with cytoplasm emerging and one nucleus at the pore. Probably three amebae have already escaped

or asymmetrical cysts with *Endolimax nana*, and, when spherical or viewed on end as spherical looks like a small four-nucleated *Endamoeba dysenteriae*. In fact Nöller⁶ placed it in the synonymy of *Entamoeba hartmanni* Prowazek but his illustrations of that so-called species do not include any figures of Kuenen and Swellengrebel's *Entamoeba tenius*. Morphologically, culturally and in its pathogenic capacity, *E. hartmanni*, in our opinion is only a small but frequent phase of *Entamoeba dysenteriae* and should not be given specific recognition.

It is different however, with the species *tenius*, which is distinguishable. We allocate it however, to the genus *Councilman* instead of *Endamoeba* (or *Entamoeba*) because of the structure of its nuclei in the matured cysts.

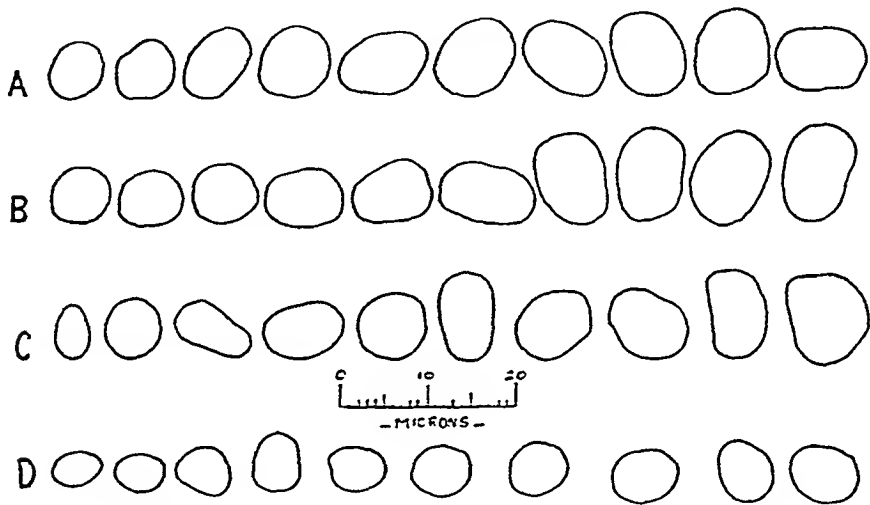


Fig 3—Cysts of *Councilmanian tenius* in outline from four different cases in man. Case A average long and short diameters 6.5 and 5.2 microns, case B, 8.9 and 6.2, case C 9.1 and 6.7, case D 9.4 and 7.4. Average of the 40 cysts 8.5 by 6.4 microns. $\times 1,000$.

COUNCILMANIA TENIUS

The following morphologic features characterize this species. The motile stages of *Councilmanian tenius* (Kuenen and Swellengrebel⁵) are small from 7 to 10 microns, with broadly rounded, clear pseudopodia, fairly active. Encysted phases are abundant in stools with one nucleated and four nucleated stages predominating, less frequently eight nucleated. The cysts measure from 3.1 by 5.7 to 8 by 10.6 microns, the average mean diameter of 500 being 7.1 microns, generally slightly

⁶ Nöller W. Die wichtigsten parasitischen Protozoen des Menschen und der Tiere. I. Teil Einführung und die allgemeine Kenntnis und die Untersuchung der parasitischen Protozoen und Abschnitt I. Die parasitischen Rhizopoden, Berlin Schoetz 1922 p 272.

of the sphere, ellipsoidal, ovate or asymmetrical to a slight degree. Glycogen is not massive, usually in several larger or numerous smaller not clearly delineated vacuoles. There are few chromatoidals, rather small, broadly ellipsoidal or ovoidal, often slightly asymmetrical or small, subspheroidal or irregular in a clear halo (of solution?). The nuclei are very faint, difficult to locate and to define because of the lack of peripheral chromatin, often subspherical or with irregularities in contour, with central or subcentral, irregular, rather large deeply staining karyosome formed by an aggregate of small granules, clearly separable in many nuclei, with greater difficulty in others. As in *Councilmania laffeyi* the karyosome may be subspheroidal, reniform ring-shaped or a semicircular row of heavy granules, but, as a general rule, under high magnification and good definition, it is seen to be an irregular aggregate of chromatin spherules. In many nuclei its granules are widely dispersed. At mitosis the karyosome moves to the periphery and it forms the typical, but faint, intradesmose as the chromosomes form, in part at least from its substance. Their number is about six, but has not yet been accurately determined.

The cysts bud less freely than those of *C. laffeyi* in the stool and are found in this condition in fresh smears and stained slides. Nuclei have been found in transit through the minute hole in the cysts and in the budded amebula attached to, or adjacent to, the parent cyst.

Due to the fact that the cytoplasm of this species destains readily in union hematoxylin, and that there is not any appreciable amount of chromatin on the nuclear membrane the cysts of this ameba have a different aspect in stained fecal smears from those of other amebas such as *E. dysenteriae* with more stainable cytoplasm and nuclear wall encrusted with black peripheral chromatin. The facts that the chromatoidals are ovate or subspherical and often small, and that the central karyosomes are rather large and in clear halos not unlike those about the decreasing chromatoidals, add to the aberrant appearance of these amebic cysts. This may lead the examiner of the smear to throw them into the discard or to regard them merely as aberrant *Endolimax nana* or even *Endamoeba dysenteriae* of the smaller phases, from 7 to 9 microns, in which the amount of peripheral chromatin is not so noticeable as in the larger phases. The large size of the central karyosomes in some cysts and the faint nuclear membrane of *C. tenuis* also give a picture suggestively like that of the nuclei of chromatin-poor *Endolimax nana* seen with the lateral blobs in face view. The similarity is heightened by the subspherical shapes of some of the cysts of *C. tenuis*.

Nothing critical is known of the pathogenicity of this species. Animal experimentation and serologic tests with pure cultures as well as clinical study of cases of pure infections by this species are needed to establish its relations to its host.

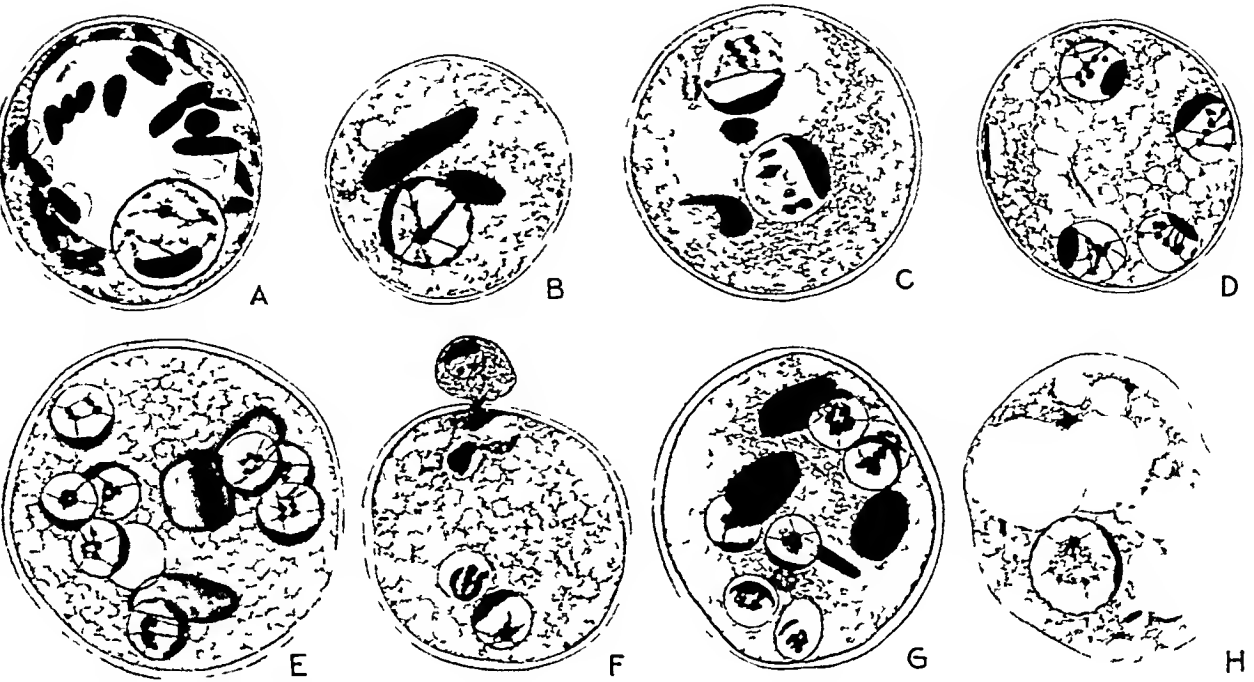


Fig 4—*Councilmanella dissimilis* sp nov from fecal smears stained in iron hematoxylin, $\times 2210$

A, mononucleated cyst with large spheroidal (probably lenticular in the plane of the section) glycogen vacuole, numerous small faintly bordered chromatoidal bodies, nucleus in early prophase, with peripheral chromatin network and heavy lateral blob

B, mononucleated cysts with two chromatoidals with asymmetrical ends, three small glycogen vacuoles, and nucleus with lateral blob, eccentric, irregular karyosome and radii

C binucleated cyst with disappearing diffuse lenticular eccentric glycogen vacuole, two small flakelike chromatoidals, nuclei in prophase with emerging chromosomes, the left with an intradesmose connected at one end with the lateral blob

D, four-nucleated cyst with diffuse vacuolation, linear remnants of the chromatoidals nuclei with heavy lateral blobs and dispersed karyosomes

E eight-nucleated cyst with diffuse vacuolation, and one small vacuole, stout, angled bordered chromatoidals, nuclei with marked lateral blobs and dispersed karyosomes

F, budding cyst with three nuclei one in the escaping amebula and chromophil cytoplasm in pore and bud. Remnant of a chromatoidal in a halo, and several other minute remnants. Nuclei with lateral blobs and somewhat dispersed karyosomes

G, cyst with seven nuclei with lateral blobs and variously dispersed karyosomes four somewhat bordered squarish or rodlike chromatoidals, and no glycogen vacuole. The cytoplasm is chromophil toward and in a small circular pore on the upper surface. Probably one amebula has already escaped reducing the eight nuclei to seven

H, motile ameba from fecal smear with retracted clear pseudopodia and nucleus with lateral blob and dispersed karyosome

The incidence of infection by *Councilmania tenuis* in man is rather high. In 7,746 examinations of about 2,587 persons made in my laboratory between Jan 1, 1927, and May 31, we recorded 239 cases, or about 9.2 per cent. Previous records in the last two years approximate this. These figures are slightly higher than is warranted by the real facts, as the number of persons is made up from our monthly totals and involves a small overlap.

The second species is one which masquerades under the cover of *Endamoeba dysenteriae*, which it resembles closely in many particulars. It is, indeed, included in some of the published figures of cysts of *E. dysenteriae*, as in those of Hartmann and Belar⁷ (1921). It may be responsible for the belief that *E. dysenteriae* sometimes goes to the eight-nucleated stage in the cyst, and that this species sometimes exhibits the appearance of budding. It undoubtedly is being reported as *E. dysenteriae* for treatment. The extent to which its presence in man and its present confusion with *E. dysenteriae* (large race) complicates the clinical picture of amebiasis and of amebic therapy can be determined only by prolonged study. It is important that this species be recognized in examination of the stool and ruled out of possible confusion with the larger race of *E. dysenteriae*, especially by critical, clinical and therapeutic investigation and comparisons of cases of pure infections by the two species singly. The characters of this species of *Councilmania* are given in the following paragraphs.

COUNCILMANIA DISSIMILIS, SP. NOV.

The outstanding features of this species are the heavy lateral blob of peripheral chromatin on the nuclear membranes, and the predominantly dispersed karyosomes in the matured cysts, the occurrence of eight-nucleated cysts and the free budding of cysts in the feces and in fresh untreated cultures.

The nucleus is typically spherical, but seems to be subject to slight deformations to a somewhat greater extent than in *E. dysenteriae* and to a smaller extent than in *E. gingivalis*. The nuclear membrane is faint, especially in cysts and in the chromatin-free parts of the wall. Its chromatin occurs in two regions, the peripheral, applied to the nuclear membrane, and the karyosomal or central, which usually is considerably dispersed.

The peripheral chromatin has a characteristic distribution. Instead of being distributed over the inner surface of the nuclear membrane in a thin layer, or scattered in small masses of subuniform or somewhat

7 Hartmann, M., and Belar, K. Die parasitischen Amöben des Menschen und der Säugetiere, in Prowazek, S. von, and Noller, W. Handbuch der pathogenen Protozoen, Leipzig, Barth, 37 fig. in text, 1921, vol. 3, p. 1295.

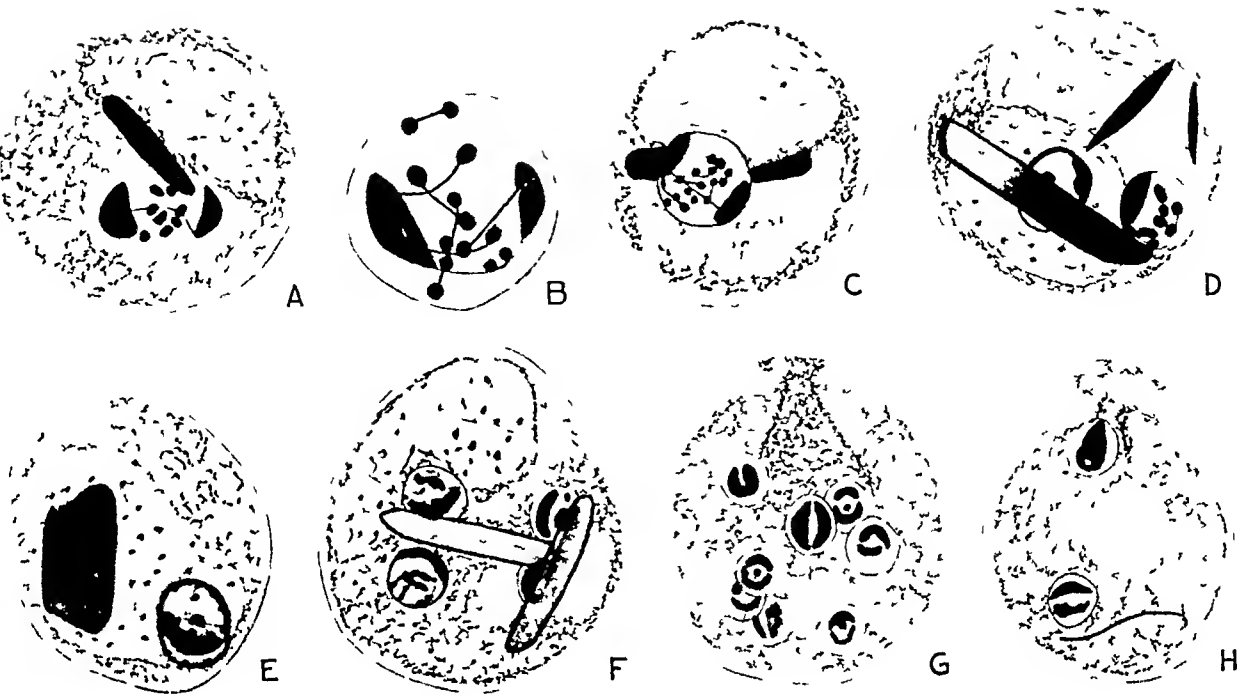


Fig 5—Cysts of councilmania dissimilis Kofoid from fecal smears Reduced from a magnification $\times 2210$ Drawings by Mrs Dora Henry

A, mononucleated cyst with large lateral asymmetrically lenticular glycogen vacuole with stained nodal network, nucleus in early metaphase with eight undivided chromosomes, and slender linear intradesmose joining two polar masses derived from the lateral blob of peripheral chromatin. Centrosomes, if present at the ends of the intradesmose, are not visible. A single rod-shaped chromatoid with ends lies below the nucleus.

B, nucleus only, from another mononucleated cyst with more advanced stage of division of the chromosomes. Note the differences in size and state of division.

C, mononucleated cyst in more advanced stage of nuclear division than figures *A* and *B*. Slender intradesmose joins ends of the polar siderophil masses. Single lateral glycogen vacuole and single chromatoid rod with squarish ends.

D, binucleated cyst with lateral glycogen vacuole, three chromatoids, the largest with markedly asymmetrical subangular ends and deeply stained peripheral layer, nuclei with lateral blobs, chromosomes are visible in right nucleus.

E, mononucleated cyst with single flattened asymmetrical chromatoid with subangular ends and dark peripheral layer. Large glycogen vacuole and nucleus with lateral blob and some chromatin in strands on the membrane are present.

F, four-nucleated cyst with two glycogen vacuoles, two rod-shaped chromatoids with asymmetrical subangular ends and peripheral siderophil layer.

G, eight-nucleated cyst with chromophil cytoplasm emerging from pore.

H, binucleated cyst with amebula emerging. Compare size of nuclei with those in figure *G*. Probably the six amebulas have already escaped.

varying size, as it is in *E. dysenteriae*, it is found in *C. dissimilis* massed mainly, or almost wholly, in one large lateral blob. This single mass is crescentic in outline, and spans almost one half of the circumference of an optical section of a nucleus when the blob is in the plane of the section. It may appear shorter than this, but in such cases it will be found usually that it is foreshortened by the obliquity of its position with reference to the focal plane. Its greatest thickness ranges from 0.14 to 0.30 of the nuclear diameter, and its width is somewhat greater. It stains intensely black because of its mass. Its inner face may show evidence of indentation or subdivision. When it lies on the upper or lower surface of the nucleus, it may be overlooked.

In the relatively infrequent binucleated stage, the lateral blobs are reduced or even absent. In some nuclei, there may be small accumulations of peripheral chromatin elsewhere than in the blob, which appear in optical section as thin blobs or scattered granules applied to the nuclear membrane. In some instances in motile forms in culture, the blob is considerably reduced in thickness, and the peripheral extension of the chromatin is increased. The most striking feature of this species is the structure of the nucleus of the mature cyst with the heavy lateral blob and faint nuclear membrane elsewhere on the nuclear surface. In the binucleated stage, because of its close juxtaposition to the preceding and following mitosis, the lateral blob is less in evidence.

The central karyosome (fig 4, D-H) is composed of a number of discrete granules which in the nuclei of the matured cyst are often rather widely dispersed. Evidence of a clear halo is not found around the karyosome as in *E. dysenteriae* (Kofoid and Swezy⁸) or of the typical spheroidal state of the karyosome so characteristic of *E. dysenteriae*. This dispersal is strikingly similar in pattern to that described for *Councilmania laffeyi* by Kofoid and Swezy (1921) and found by Kessel (1924) in *C. muiri* and *C. decuman* from rats and mice.

The number of nuclei in the cyst depends on the age of the cysts. In some stools, mononucleated cysts with large nuclei are abundant, many in the prophases of mitosis. In others, four-nucleated cysts predominate with few mononucleates and binucleates. Less frequently and generally in stools with mature four-nucleated cysts, a few cysts with eight nuclei occur. This number, as that of the four-nucleated cysts, is reduced by budding and the successive escape of amebulas with nuclei from the cyst in some instances. Four-nucleated cysts are frequently seen with prophases of mitosis in their nuclei.

We have never seen this increase in the number of nuclei from four to eight in the cysts in *Endamoeba dysenteriae*. The cases, stools and smears in which the eight-nucleated cysts occur in *C. dissimilis* are,

⁸ Kofoid and Swezy 1924, plate 17, figs 32-43

however, so infrequent that this feature is available only occasionally for diagnostic purposes in examinations of stools. It is, however, of classificatory value as a mark of a distinct species.

The number of chromosomes in this species is eight. The chromosomes can be counted in the prophase as split, meridional, faintly stained structures on the nuclear membrane and at the late metaphase as bilobed or divided masses of unequal sizes. The material of the lateral blob forms around the polar centrosomes and perhaps contributes to the faint intradesmose joining them.

The glycogen vacuole is characteristically eccentric in location, best seen at its maximum development in mononucleated cysts, often contains throughout its entire area in stained cysts a fine reticulum with stained nodal granules and may fill nearly one half of the cyst. It is asymmetrically lenticular in contour and crowds close to the periphery. It may be broken up into smaller areas of equal or varying size with somewhat diffuse margins, often larger in the periphery of the cyst. The lateral position of this vacuole is correlated with the crowding of the single nucleus to one side.

The chromatoidal substance typically stains a dense homogeneous black in iron hematoxylin, but in this species exhibits considerably more variability than in *E. dysenteriae*. Black bordered chromatoidal bodies with paler centers are frequent, and washed out pale bodies also occur but without borders. Likewise, there is rather more than the usual evidence of halos (or shrinkage?) about these bodies.

The shape and size of these bodies vary greatly according to the phase of their formation, either near the surface of the large glycogen vacuole in the early period of their history or as slender rods in halos of solution in their last stages. In the earliest phases they are oval or asymmetrically ellipsoidal in outline, not over 2 to 2.5 times as long as wide, rounded but more or less asymmetrical at the two ends and often flattened against the glycogen mass to a thickness half their width. There may be over forty such bodies crowded about the surface of the glycogen mass when it is large. The number present in later stages decreases rapidly, until in the four to eight nucleated stage there may be only from one to four present, and in the old cyst, none. When the glycogen and the chromatoidal substances are small in amount and also as the cysts with much chromatoidal substances age, there is often only a small number or a single large chromatoidal body. The largest may be as long as the diameter of the cyst and 0.2 of the length in width, or short and stout, 0.5 as long as wide, or even squarish. In favorable views and probably in all cases, the two ends are asymmetrical and singly or doubly obliquely faceted with rounded angles. The squarish and rectangular types are usually flattened, the longer types more

rounded. Whatever the position, careful focusing often reveals this terminal asymmetry and angularity. The last remnants are slender rods or irregular flakes.

The process of budding of the cysts occurs freely in the stool, as in *C. laffleurii*. Budding cysts are found in fresh smears not under the least external pressure, in stained smears, in cysts formed in culture tubes, and the process of the escape of the amebulas has been watched under the microscope. The pore through which the budding amebulas escape is from 0.35 to 0.50 the diameter of the nucleus of the four-nucleated cysts. The area of the cytoplasm leading toward the pore stains a little more deeply as though condensed, as may also that of the amebula outside of the wall of the cyst. This darker staining, as a rule, is not so marked as it is in *C. laffleurii*. Budding has been observed in cysts with one, four, and eight nuclei.

The cysts are rather uniformly close to the spherical form, whereas in *C. laffleurii* they tend somewhat more toward the broadly ellipsoidal

TABLE 1.—Range and Diameter of Cysts in Cases of *C. Dissimilis*

| Number | Range | Average | Diameters of Extremes |
|--------|--------------|---------|-----------------------|
| 29076 | 11.6 to 11.9 | 13.1 | 11.6 by 13.3 |
| 52260 | 11.6 to 11.9 | 13.1 | 11.9 by 19.2 |
| 63771 | 11.6 to 11.9 | 12.9 | 13.3 by 16.6 |
| 63885 | 13.3 to 16.6 | 14.1 | 11.6 by 16.6 |
| 71311 | 11.6 to 16.6 | 11.3 | 11.6 by 11.9 |

contour. The range and average diameter noted of ten cysts and the most extreme departure from the spherical in five different cases of *C. dissimilis* are given in table 1. The diameter used when the cyst was not exactly spherical was the longer one.

Councilmania dissimilis is less frequent in man than either *C. laffleurii* or *C. tenuis*. In 7,746 examinations of about 2,587 persons in my laboratory between January 1 and May 31, there were eleven cases of infection, or about 0.4 per cent. We have seen probably more than 100 cases. The cysts are often abundant in the stool, not infrequently as many as five cysts may be seen in a single oil immersion field, indicating unusually heavy infections. As in the cases of other intestinal infections, pure infections by this species alone are rare. It usually occurs with one or more of the other commoner *Protozoa*. It persists in varying frequency during any period of examination, and may decrease markedly or even disappear for a time, and then return in the stools.

The grounds for the specific separation of this ameba from *E. dysenteriae*, with which it is at present confused, are primarily the eight chromosomes as over against the six in that species, the distinctive large blob of chromatin, dispersed karyosome, eight nuclei in the cyst

and the frequency of budding in the stool. Clinical and cultural grounds are given in the following parts of this paper.

The grounds for placing the organism in the genus *Councilmama* are primarily the predominantly dispersed karyosome, a feature of nuclear structure in the resting nucleus of the matured cyst which characterizes all species of this genus. The slight tendency to asymmetry or off-the-sphere shape of the cyst, the frequent budding process in the stool and the chromophil condition associated with budding are also developed in the other species of this genus. In the genus *Endamocba* (= *Entamocba*), the karyosome is typically solid and spherical. Neither chromophil ridges nor budding in the fresh stool has been seen by us in what we regard as *E. coli* or in *E. dysenteriae*. This process must, of course, occur in those species also, in some form, whenever and wherever the contents of the cyst escape, but this has not been seen by us in stools either fresh or old or in stained preparations.

The relation of *C. dissimilis* to the so-called large race of *E. dysenteriae* is at present problematic. It has thus far probably been included in it. In our own material it by no means constitutes the whole of it, though it does form a considerable sector of it, not less than 25 per cent. Our extensive records and collection of slides had not been reviewed on this point at the time this paper was written. It is of sufficient frequency to enter into the problems of microscopic determination of specific infections, clinical observation, symptomology and therapy of human amebiasis.

SUMMARY

Nuclear structure in matured cysts of human intestinal amebas in fecal smears stained in iron hematoxylin afford a critical, easily available and satisfactory basis of specific determination of the different species occurring in man.

The nuclear structure is also available as one basis for generic distinctions. *Endamocba* has predominantly nuclei with a solid spherical karyosome. *Councilmama* has predominantly nuclei with a more or less dispersed karyosome in the nuclei of easily matured cysts. Mitotic and metabolic phenomena modify the nuclear picture in the motile phase and in early phases of the encysted stage.

There are two amebas in human stools that have masqueraded under the cover of other species because of resemblances to them. *Councilmama tenuis* (described by Kuenen and Swellengrebel 1917, as *Entamocba tenuis*) belongs to *Councilmama* because of its dispersed karyosome. It has rather small 7.1 (from 3.1 by 5.7 to 8 by 10.6) microns, somewhat asymmetrically rounded cysts with one, two, four, and eight nuclei, diffuse glycogen vacuole, few rounded to short rod-shaped chromatoids, nuclear membranes often deformed with little or no periph-

eral chromatin. Cysts are found budding freely in fresh stools. Both cytoplasm and nuclei stain faintly. There are motile stages with clear pseudopodia. The percentage in 2,587 persons is 9.2 per cent.

The second ameba, *Councilmania dissimilis*, has been confused with the large race of *Endamoeba dysenteriae*. It has clear pseudopodia in life. The glycogen vacuole is usually single at first, very large, eccentric and may show a stainable network, but later breaks up into smaller vacuoles. The chromatoids are large, often asymmetrically angled, but sometimes squarish. Fifty cysts average 13 microns in diameter and range from 11.6 to 16.6 microns. Some are ellipsoidal. The percentage of infection in 2,587 persons was 0.4 per cent. The cysts are nearly spherical, have one, two, four, and eight nuclei, with peripheral chromatin massed in one large crescentic lateral blob on the membrane, karyosome in mature cysts, typically dispersed or made up of large granules.

I am indebted to Miss Inez Smith, M.A., examiner in my laboratory, for the first detection of the distinctive characteristics of *Councilmania dissimilis*, to Olive Swezy, Ph.D., and to Mrs. Dora Henry, M.A., for drawings of this species, to Miss Alfreda Kirsch, M.A., for drawing of *C. tenuis* and to the Board of Research of the University of California, to Miss Ellen B. Scripps, and to other friends of the University for grants in aid of this research.

CULTURE METHODS, ENCYSTMENT AND EXCYSTMENT OF *COUNCILMANIA DISSIMILIS* KOFOID, IN CULTURE

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Since Sept 25, 1925, for a period of twenty months, *Councilmania dissimilis* has been grown in Professor Kofoed's laboratory in mixed cultures with bacteria in various kinds of mediums mentioned. It grows abundantly in carefully made mediums at a constant temperature of 37.5 C, however, the abundance varies with the different strains and even with the same strain. This would be expected, since the bacterial flora is never the same for any two strains, and in the cultures of the same strain there is variation of growth of the bacteria because the different kinds of organisms present vary as to the time of their separate lag periods, these, in turn, affect the lag period of the ameba.

From the stools of six patients, ten separate strains of *Councilmania dissimilis* Kofoed have been obtained in cultures in the Protozoological Laboratory of the University of California.

COMPARATIVE MORPHOLOGY

Councilmania dissimilis continues to reveal its morphologic characteristics even after long cultivation in artificial mediums, however, the large peripheral blob on the nuclear membrane of the resting nucleus, even though present, is not always as noticeable, since in culture amebas the stain decolorizes more easily than in nuclei of specimens in stools. The resting nucleus, as seen in figure 1, A, B, C, and D shows a linen network, like a spider's web, radiating out from the granular, dispersed karyosome. This network contains tiny chromatin granules, one at each junction of the fibers. In addition to the large curved peripheral blob, there are often smaller blobs distributed on the nuclear membrane.

Many division stages are visible on culture slides, and eight chromosomes have been counted on a number of spindles in dividing amebas in cultures as shown in figure 1 D of a nucleus in the anaphase with eight pairs of chromosomes. This fact definitely distinguishes *C. dissimilis* from *E. dysenteriae*, which has only six chromosomes (Kofoed and Swezy¹ 1925).

Although the pseudopods appear clear and distinct from the granular endoplasm in living amebas when stained they show an alveolar struc-

¹ Kofoed A. and Swezy Olive. On the Number of Chromosomes and the Type of Mitosis in *Endamoeba dysenteriae*, 1925

ture similar to that of the main body of the ameba, but they stain lighter and show distinctly the boundary between endoplasm and ectoplasm (fig 1, A)

Figure 1, *E* and *F* represent cysts of the same strain produced in culture a year and a half old. The large nucleus shown in figure 1, *E* is not far removed from the precystic stage. It reveals the same characteristics as the resting nucleus of the motile forms. The nuclei of the cysts are similar to those in the original description given by Kofoid, except in the smaller amount of chromatin of the blob and karyosome.

These amebas in culture vary in size from 11.5 to 14 microns in diameter in the encysted stage.

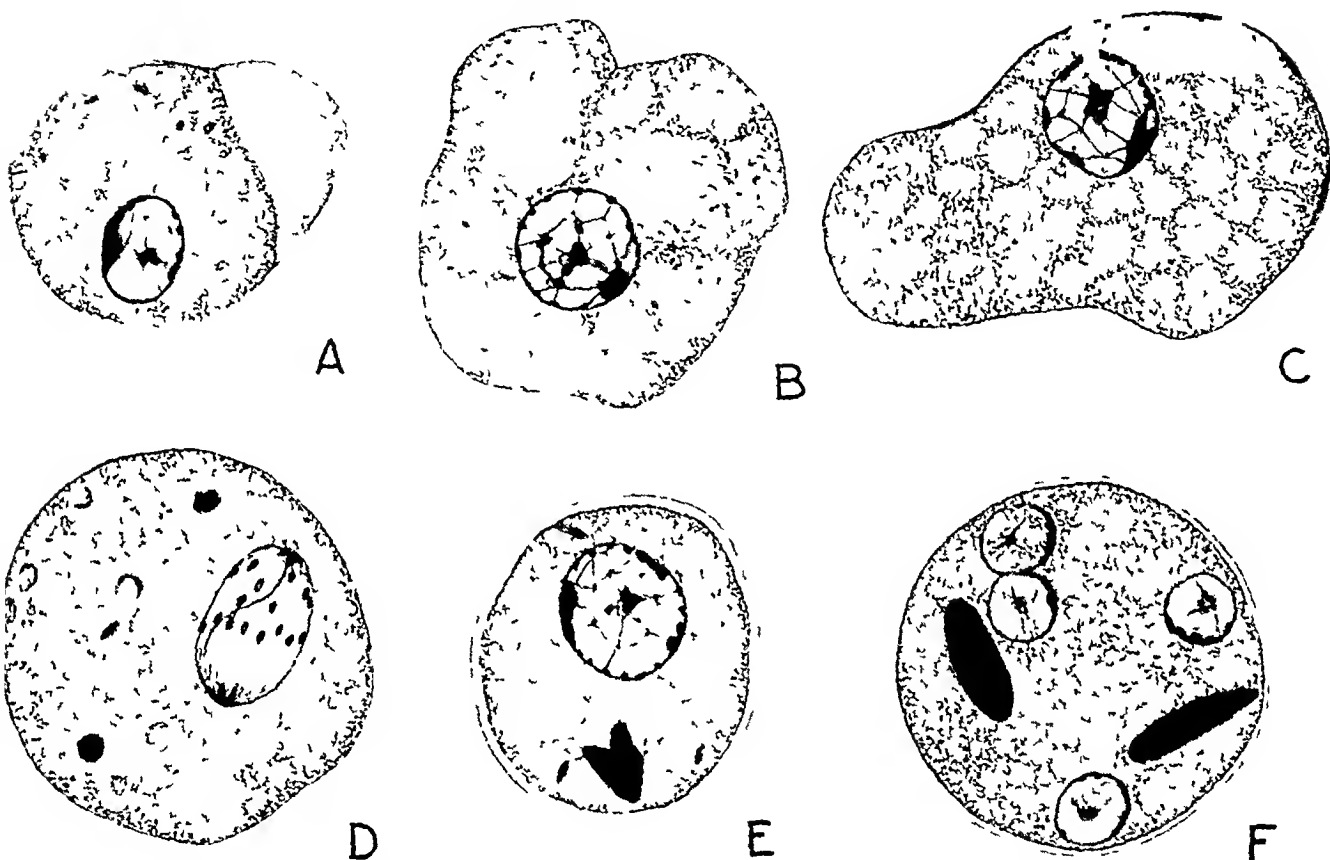


Fig 1—*Councilmanella dissimilis* Kofoid from cultures in vitro. Reduced from a magnification $\times 3250$.

A, motile form with broadly rounded pseudopods.

B and *C*, motile forms with resting nuclei. Note the dispersed karyosome, large curved peripheral blob in addition to smaller chromatin blobs on the nuclear membrane, also a network of linen fibers radiating from the karyosome.

D, motile form in mitosis with sixteen (eight pairs) of chromosomes at early anaphase. Note also the ingested bacteria. The delicate sigmoid line joining the polar centrosome is the intradesmose.

E, a precystic phase or early mononucleated cyst with large resting nucleus with lateral blob and the two small chromatoids. A few bacteria still remain undigested even though the wall of the cyst has formed.

F, a four-nucleated cyst with two asymmetrically pointed chromatoids.

MEDIUMS

The following mediums have been used to good advantage Locke's-egg-albumin, Locke's-egg-serum, Locke's-serum, Locke's-egg-blood and Vogel's² starch-agar slants with buffered Ringer's or Locke's solutions added to them. The Locke's solution used is the modified formula given by Kofoid and Wagener,³ they also added 0.5 per cent defibrinated blood to the Locke's solution used in covering the egg slants. For the Locke's-egg-blood medium, rat and rabbit blood have proved satisfactory, but rabbit blood is preferable, since it is more easily obtained in large quantities. Human, beef and rabbit serums have been tried. In the serum mediums used, the amebas are granular and extremely variable in size. Human serum gave better results than any of the other serums.

Drbohlav's formula⁴ Ringer's solution plus 1 per cent dextrin is valuable for eliminating *Blastocystis hominis* and some flagellates such as *Chilomastix davamei* and *Entomonas hominis*, it also helps in eradicating some undesirable amebas.

COMPARATIVE EXPERIMENTS OF *COUNCILMANIA DISSIMILIS* AND *ENDAMOEBIA DYSENTERIAE* IN VARIOUS MEDIUMS

Cultures of *Councilmania dissimilis* and *Endamoeba dysenteriae* in the various mediums already mentioned, have been compared from time to time, during a period of fifteen months. In spite of many variables in these cultures, mixed with bacteria, some striking differences have been noted in three different strains of each kind of these amebas, all strains of each species giving the same characteristics for each experiment.

Councilmania dissimilis grows well indefinitely in Locke's-egg-albumin, while *Endamoeba dysenteriae* flares up, increasing considerably in numbers for the first twenty-four hours of the first transplant, it then continually decreases and many amebas die, until at the end of forty-eight hours there are fewer amebas than were originally put into each tube. This leaves a smaller number of amebas for the second transplant. This reduction continues from transplant to transplant until the amebas die out entirely by the end of two or three weeks in the forty-eight hour interval.

2 Vogel, H. Ueber Kulturen der Ruhramoebie und deren Beeinflussung durch Yatren, Arch f Schiff-u Tropen-Hyg **31** 74, 1927.

3 Kofoid, C. A., and Wagener, Edna Hannibal. The Behavior of Endamoebae Dysenteriae in Mixed Cultures with Bacteria, Univ Calif Pub Zool **28** 127, 1925.

4 Drbohlav, J. Culture d Entamoeba coli. Ann de Parasitologie **3** 364 1925.

Councilmania dissimilis also grows much better in Locke's-egg-serum than *Endamoeba dysenteriae*. *C. dissimilis* persists for a much longer time in this medium than *E. dysenteriae*, which fails to reproduce after the first flare-up and gradually dies out. Of the many tubes cultured, nine of *C. dissimilis* to one of *E. dysenteriae* reproduce well in twenty-four hours. For the first forty-eight hours, however, there are twice as many positive cultures of *E. dysenteriae* as in twenty-four hours, so the ratio at the end of forty-eight hours is on the average of nine tubes of *C. dissimilis* to two tubes of *E. dysenteriae*. After a few transplants, only *C. dissimilis* survives. Human serum was used for these experiments, and approximately the same number of amebas were put into each tube for each experiment.

ENCYSTMENT

Since twenty-four hour cultures contain more amebas than those forty-eight hours old, it was believed that by transplanting every day for a time, it would be possible to obtain the entire life cycle of *Councilmania dissimilis*. It was thought best to use Locke's-egg-blood medium, to have fresh rabbit blood on alternate days and to transplant every day for three days, observations of results to begin on the fourth day after making another transplant. Since the blood medium produces conditions approximating more nearly those existing in the human body, it was chosen in preference to that containing egg albumin. Observations on the amebas were made on cultures from one to forty-eight hours old, both from permanent slides and from mounts in iodine eosin.

This experiment has been performed four different times. Twice strains of *Endamoeba dysenteriae* were used by way of comparison in addition to cultures of *Councilmania dissimilis*. For these experiments, five different strains of *Councilmania dissimilis* and three different strains of *Endamoeba dysenteriae* have been used.

In every experiment, encystment resulted in cultures of *Councilmania dissimilis*. Cysts of *Endamoeba dysenteriae* were not found in any tubes.

EXCYSTMENT

The stool material from which nine of the strains were cultured contained many cysts and few motile forms, two of them did not appear to have any motile forms. In each case, prolonged search did not reveal cysts in the cultures by the end of forty-eight hours after the original inoculation, but numerous active amebas were present.

Culture cysts produced in the foregoing experiments also excysted if allowed to remain in the incubator without being disturbed for about forty-eight hours after formation. Budding cysts have been found in original material and in cultures from time to time.

SUMMARY

1 Ten strains of *Councilmaniana dissimilis* have been cultured in various mediums, principally in Locke's-egg-blood and Locke's-egg-albumin. It also grows in serum without slants according to Craig's⁵ method. This ameba has been cultured for the past twenty months in this laboratory. Cultures of *C. dissimilis* compared with those of *E. dysenteriae* show that both amebas grow equally well in Locke's-egg-blood, whereas in Locke's-egg-albumin, *C. dissimilis* grows indefinitely but *E. dysenteriae* dies out after a few transplants. The ratio of survival of *C. dissimilis* and *E. dysenteriae* in Locke's-egg-serum is nine tubes of the former to two of the latter for the first forty-eight hours. *C. dissimilis* will also persist for a long time in Locke's-egg-serum, and *E. dysenteriae* lives in it for only a few transfers.

2 Encystment of *Councilmaniana dissimilis* has been produced in cultures by daily transplanting into Locke's-egg-blood, using only fresh blood. These same methods have failed to produce cysts of *Endamoeba dysenteriae* in our cultures.

3 Encystment of *C. dissimilis* has been produced from specimens of stools in culture and from cysts that were experimentally developed in cultures.

4 *Councilmaniana dissimilis* in culture has eight chromosomes, a large curved peripheral blob and a dispersed karyosome, which are not characteristics of *E. dysenteriae*.

5 Craig, C. F. A Simplified Method for the Cultivation of Endamoebae. *Histologica*, Am J Trop Med 6:333, 1926.

PRESENTATION OF CASE OF INFECTION WITH COUNCILMANIA DISSIMILIS KOFOID

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The following case represents one of the few relatively simple infections with *Blastocystis*, *Giardia enterica*, the three species of *Councilmania* and *Endolimax nana*. It offers the advantage of not having an admixture of *Endamoeba dysenteriae* or *Endamoeba coli* infections. Therapeutically, it is interesting because of the susceptibility of *Giardia enterica*, *Councilmania laffeyi* and *Councilmania tenuis* to full doses of antimony trioxide and the resistance of *Councilmania dissimilis* to this medication. It is also interesting to see both *Councilmania dissimilis* and *Endolimax nana* disappear after doses of stovarsol. It is to be borne in mind that we feel it is too early to judge of the thoroughness of the eradication, and that rechecking of the physical and laboratory observations is necessary for a period of two years before a presumptive "cure" can be granted. At present, the return of a large mononuclear count of 8 per cent suggests that the eradication is possibly not so complete as the examinations of the stool would lead one to believe.

REPORT OF CASE

A man, aged 38, white, married, who presented himself in July, 1926, said that a definite pain in the upper portion of the left side of the abdomen came on after attending a picnic in May, 1924. The pain continued, but remission occurred for periods as long as six, eight or ten months. There had not been complete relief since December, 1925. Birth had been normal, the patient had heard that his mother was lacerated at confinement. He had been breast fed for the first nine months of infancy. During childhood he had had whooping cough, measles, chickenpox and scarlet fever, but he had not had especially severe attacks. At 17, he had three severe attacks of appendicitis, the last ending in operation with drainage. Drainage caused a hernia, which was successfully repaired. His tonsils were "clipped" and later enucleated. A deviated nasal septum was repaired in 1911. He had had a light attack of influenza in 1918. He did not say that he had had venereal disease.

Residence for a period long enough for the eating of a meal had included France, Italy, Switzerland, Germany, England, Canada and practically all of the states of the United States. The father died at the age of 62 of cancer—"beginning in the neck." The patient could not be more specific. The mother, aged 63, on whom hysterectomy had been performed, was alive and well. One brother was alive and well.

Two sisters were alive—the elder was well, the younger had pulmonary tuberculosis and had recently had a collapsing operation of the chest.

The patient's wife, slightly younger, was alive and well after treatment for *Councilmania* infection. Two small sons, aged 3 years and 6 years, were alive and well. The elder son had had moderate adenopathy of the neck.

The patient's status was as follows. The appetite was excellent—the patient said “too good.” The digestion was normal, that is, food did not cause distress. The bowel habit had been one evacuation about every thirty-six hours. Recently, it had changed to one evacuation every twenty-four hours. There was seldom nocturia. The patient slept soundly, not less than eight hours—and rose refreshed. He estimated his muscular strength at normal. His weight had not changed much in a year, but he thought that it might be increasing slightly. He was not especially nervous, although he had been depressed occasionally during the past year. He considered his sexual powers normal, or but slightly below normal.

Examination—The physical examination revealed a well nourished man, aged 38, with a temperature of 98 F. The pulse rate was 84, the respiratory rate was 16 plus, and the blood pressure was 174 systolic and 104 diastolic. These rates were normal and were taken while the patient was in a supine posture. He was 68½ inches (173.9 cm) in height and weighed 146 pounds (66.2 Kg), his previous maximum weight being 152 pounds (68.9 Kg). The hair, skin and vertebral column were normal. The eyes were normal, and glasses were worn only occasionally. The conjunctivae were slightly and chronically injected. A few small meibomian cysts were present. The muscular movements and light and accommodation reflexes were normal.

The drum of the left ear was definitely sclerosed, the drum of the right ear was normal. The hearing was as follows: Right $\frac{\text{normal}}{\text{normal}}$, left $\frac{0}{0}$.

The airways of the nose were narrow. There was a slight chronic rhinitis. The teeth were well preserved and well kept. There were a few small gold fillings. The tonsils had been removed. The pharynx showed a chronic inflammation with dilated vessels and a mild “blobbing” of the mucosa. The neck was normal. The shape of the chest was symmetrical. The antero-posterior diameter was less than normal, resulting in a flattening.

The mammae and nipples were normal. The lungs did not show signs of activity of any pulmonary lesion. Observations from inspection, palpation, percussion and auscultation were normal. The point of maximum impulse of the heart was within normal limits in the fifth interspace. The area of cardiac dulness was of normal size. The heart sounds were normal.

Examination of the abdomen revealed an old appendectomy scar with evidence of repair. The liver was from 17.5 to 19.5 cm in diameter in the right midclavicular line. The edge of the liver was palpable from two to three fingerbreadths below the costal margin. The spleen was not palpable. The cecum was slightly sensitive on palpation. The area of the sigmoid colon was sensitive on palpation. The left flank was also sensitive to pressure on palpation. The inguinal areas were normal. The genito-urinary system showed normal conditions.

The nail of the great toe on the right foot was nodular. There was a small scar over the left patella. The patellar reflexes were equal and normal, and the anterior and longitudinal arches were normal.

On entrance to our service, examination of a single specimen of urine taken in the afternoon showed that it was amber and clear with a specific gravity of 1.022. The reaction was acid. There was a faint trace of albumin with the heat and acetic acid test. Benedict's test did not reveal dextrose, indican was not found.

Microscopic Examination—Examination of a centrifugalized specimen revealed occasional leukocytes, one hyaline cast, no cysts, an occasional squamous and spherical epithelium, and no red blood cells or bacteria

A recheck of the urine one month later did not show any albumin

A recheck of the urine eleven months later showed a light amber, clear specimen, 2,440 cc in twenty-four hours, with a specific gravity of 1.012. The reaction was slightly acid. No precipitate of albumin occurred with heat and acetic acid test. Neither dextrose nor indican were found. There was 29.2 Gm of urea.

Microscopic examination of a centrifugalized specimen revealed an occasional leukocyte, no casts or crystals, an occasional squamous, and spherical epithelium, no red blood cells or bacteria.

The serological observations during blood Wassermann test were as follows: cholesterinized beef heart antigen, (— — —), acetone-insoluble antigen, (— — —), and alcoholic extract antigen, (— — —).

Examination of the blood on entrance to the hospital revealed erythrocytes, 5,075, per cubic millimeter, morphology, normal, immature and degenerate types, none, hemoglobin (Dare method), 90 per cent, color index, 0.9, and leukocytes, 9,400 per cubic millimeter.

The differential count revealed neutrophils, 56.3 per cent, large mononuclears and transitionals (combined count), 8 per cent, lymphocytes, 35.3 per cent, eosinophils, none, basophils, 0.33 per cent, immature and degenerate types, none, and blood parasites, none.

A recheck of the complete blood count three months later showed erythrocytes, 5,000,000 per cubic millimeter, morphology, normal, immature and degenerate forms, none, hemoglobin (Dare method), 88 per cent, color index, 0.8, leukocytes, 8,800 per cubic millimeter, neutrophils, 50 per cent, large mononuclears, 5 per cent, lymphocytes, 44.3 per cent, eosinophils, 0.33 per cent, basophils, 0.33 per cent, immature and degenerate types, none, and parasites, none.

A recheck of the complete blood count eleven months later showed erythrocytes, 5,010,000 per cubic millimeter, morphology, normal, no anisocytosis, immature and degenerate forms, none, hemoglobin (Dare method), 90 per cent, color index, 0.9 and leukocytes, 8,800 per cubic millimeter.

The differential count revealed neutrophils, 51.3 per cent, large mononuclears, 8 per cent, lymphocytes, 4 per cent, eosinophils, 0.33 per cent, basophils, 0.33 per cent, immature and degenerate types, none and parasites, none.

Bacteriologic studies of the feces two months after entrance to the hospital showed consistently in three different examinations only lactose fermenters. Six months after entrance, culture gave acid in lactose. A week later, a gram-negative, nonlactose fermenter was picked up with the following reactions and description: gram-negative rod, nonlactose fermenter, arabinose, plus, maltose, plus, mannite, plus, xylose, plus, dextrose, plus, sucrose, plus, salicin, plus, milk coagulated, hydrogen sulphide, plus, nitrates reduced and indol. An autogenous vaccine was prepared from this organism.

Sigmoidoscopic Examinations—Examinations were made on the following dates with the recorded results indicated:

July 24, 1926 Dilated vessels moderate "blobbing"—meaning by this term a heaping-up process, a coarse granulation, such as one sees in the post-pharyngeal wall in the presence of a chronic inflammation, mucus (free). A diagnosis of chronic colitis was made.

July 26 Hyperemia, dilated vessels both fine and moderate in size, a moderate scattered "blobbing" A diagnosis of chronic colitis was made

September 16 Hyperemia, dilated vessels, definite scattered "blobbing" A chronic colitis was diagnosed with little evidence of recession

April 19, 1927 Dilated vessels, coarse "blobbing" A diagnosis of chronic colitis was made The principal evidence of recession lies in a diminished hyperemia

Examinations of the Stool—Examinations of the stool in this case were made by Professor Kofoed and Miss Virginia Hall at six different intervals, with a total of twenty-nine stools shown in table 2

TECHNIC OF SIGMOIDOSCOPY

The instrument, a specially built Cameron sigmoidoscope, with an excellent telescopic attachment, is lubricated well and gently inserted, pointing at first at the patient's umbilicus The only preparation is evacuation The results are read ahead of the distal end of the instrument, and inflation occurs only spontaneously at atmospheric pressure With care and the exercise of patience, the instrument can be inserted easily in many cases as high as 14 to 17 inches (35.4 to 42.55 cm) from the anal splimeter In some spastic cases, a single dose

TABLE 2—*Examination of the Stool*

| Date | Number of Stools Examined | Organisms, Number of Stools Infected | | | | | |
|-----------------|---------------------------------|--------------------------------------|---------------------|----------------------------|-------------|-------------------|-------------------|
| | | Blasto- cysts | Giardia enterica | Councilman- ia latifera | C tennis | C dis- similis | Endolimax nana |
| July 7-10, 1926 | 5 | 4 | 1 | 2 | 1 | 2 | 2 |
| July 23-29 | 6 | 6 | 0 | 1 | 2 | 3 | 5 |
| August 4-9 | 6 | 1 | 0 | 0 | 0 | 1 | 1 |
| August 21 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| February 15-21 | 6 | 4 | 0 | 0 | 0 | 4 | 2 |
| April 25-28 | 5 | 1 | 0 | 0 | 0 | 0 | 0 |

of morphine sulphate (one-eighth grain [0.008 Gm] to one-sixth grain [0.010 Gm] with atropine sulphate one two hundredth grain [0.0003 Gm] hypodermically injected) or a day's medication with benzyl benzoate (20 drops in water every four hours for twenty-four hours) is needed as preparation

Occasionally some grade of prolapse of the rectal mucosa or even a mild redundancy makes insertion more difficult

The use of the customary inversion table, breathing by the patient as directed, inflation in rare cases, help one in these more difficult cases

A few of the English writers have somewhat doubted the necessity of the inversion table—in our experience it is invaluable, and its use is the first step in converting sigmoidoscopy from an uncertain and obscure and coarse procedure into one to which the most sensitive patient can be subjected with precision

Examination for intestinal parasites showed only the occurrence of *Councilmania dissimilis*

TREATMENT

The first treatment undertaken was with antimony trioxide, chemically pure, given in gelatin capsules in a dose of $2\frac{1}{2}$ grains (0.162 Gm) three times a day after meals, the first week—then increased to two capsules three times a day after meals, till the total quantity of 300 capsules were taken

In using antimony trioxide, we have found it necessary to test all material for the presence of arsenic. A number of batches of the drug have been discarded because of the presence of minute traces of arsenic.

Because of the chronic colitis present, installations of iodoxy quinoline sulphonic acid (1.75 Gm. in 250 milliliters of water at 105 F.) were begun and given every forty-eight hours till sixty-five doses had been given.

Two months after entrance, sodium cacodylate in 13 per cent solution in 1 milliliter doses was given hypodermically two to three times a week.

A recheck of the feces four months after the patient's entrance to the hospital showed again the presence either anew or continued of *Councilmania dissimilis*.

As *Councilmania lafleuri*, in our experience, has been readily susceptible to antimony trioxide, we decided with this *Councilmania dissimilis* to use cetarsonsone stovaisol (3 acetylamine, 4 hydroxy-phenylarsonic acid) in the original tablet, in dose of 0.25 Gm., the total number being 30. One tablet was given twice a day during the first day, then one tablet three times a day after meals, with water freely, till all were taken. Contrary to possible expectation, there was no reaction to this form of arsenic.

Occasionally we have used these tablets crushed and put up in enteric coated capsules—i.e., coated with phenyl salicylate. It was more with the idea of minimizing the irritation caused by the gastric mucosa that the enteric phenyl salicylate coat was used, since they do not act in an acid medium, but rather in an alkaline one. Raiziss¹ of the Dermatological Research Laboratory of Philadelphia is responsible for this statement.

It is curious that while this patient showed a trace of albumin in his urine on entrance, there was no evidence of irritation following the use of the acetarsonsone. Many other patients, however, have shown definite evidence of irritation after moderate use of it.

The reactions in one instance in a man weighing between 150 and 165 pounds (68 Kg. to 74.8 Kg.) were of the nitritoid variety and occurred after the ingestion of one-half tablet or 0.125 Gm. of acetarsonsone. The rest of the unfavorable reactions were of the type incidental to poisoning with arsenic. A macular rash of skin and mucous membrane, fever, intense aching and desquamation occurred.

A woman suffering from arthritis deformans and of about 150 pounds weight, had intense desquamation from head to foot after a

¹ Raiziss and Gayron. Organic Arsenical Compounds, New York, The Chemical Catalog Company, Inc., p. 360, J. Am. Chem. Soc. **43**: 583, 1921. Farb. M. L., and B. U. S. P. 1077, 462. Christiansen. J. Am. Chem. Soc. **44**: 2340, 1922.

dosage of 0.25 Gm (1 tablet) daily for five days. This patient's enlarged liver and inability to gain weight on fats was suggestive of hepatic incompetency. This suggestion became more certain when the arsenic did not cause so brisk a reaction.

COMMENT

A discussion of this case of *Councilmania dissimilis* infection should emphasize a few simple points.

In the first place, contrary to the majority of infections with *Endamoeba dysenteriae* of such long standing, the enlargement of the liver is not pronounced. In the presence of *Endamoeba dysenteriae* infections of this standing it is common to find livers with a midclavicular diameter of the right lobe of from 21 to 27 cm., and a projection of the edge of the liver below the costal margin of from three to five finger-breadths.

The other notable observation has been in the percentage of large mononuclears in the blood count. We found 8 per cent, early, and after some treatment, 5 per cent. Our last percentage, taken recently, was again 8 per cent. A relative increase in the percentage of large mononuclears is common and seems to be present rather consistently in both *Endamoeba dysenteriae* and the various *Councilmania* infections. The occurrence of a chronic colitis is characteristic of both *Councilmania* and dysentery amebic infections. It is difficult to differentiate between the two clinically, and one usually has to avail himself of the history and the behavior of the liver as checks in order to form an opinion as to whether the case is clinically one of *Councilmania* infection or one of infection with *Endamoeba dysenteriae*.

In regard to the bacterial commensals, we have found it of advantage to classify them first as to whether or not they are lactose fermenters and then also to decide whether they fall within the putrefactive or the saccharolytic group. For the time being, that is within the last nine months, since October, 1926, we have been making autogenous vaccines from the nonlactose fermenters. Occasionally, however, we have made autogenous vaccines from the lactose fermenters for treatment in these cases of chronic colitis.

Nine months' experience with this type of vaccine therapy as an adjunct in the care of these patients has hardly justified an opinion, but it can be stated that we have seen in this length of time a sufficient number of patients benefited by the vaccine therapy to warrant our continuing the labor and expense of our work.

It is not uncommon to find a patient improving after the eradication of his protozoan infection and finding some degree of his symptom complex continuing. In addition, the patient in this case has continued to improve on vaccine therapy until complete recovery has occurred.

In regard to the use of iodoxy quinoline sulphonic acid, it is interesting to note that we have had four years of experience with it in Berkeley, and that we have not seen any case that convinced us of its ability to eradicate well established infections with either of the three species of *Councilmania* or with *Endamoeba dysenteriae*

I have found it an excellent adjunct, however, in the treatment of patients with chronic colitis, which is so prevalent, and have found it much more efficacious than quinine solution, the various oils and other remedies

It is, however, by no means innocuous in its properties. We have seen a number of persons show definite and intense irritation of the bowel as a result of its use. We have also seen a series showing thyroid hyperactivity from the use of iodoxy quinoline sulphonic acid

We feel from our own experience that it is not a drug to be trusted without adequate observation of the patients. It is an efficacious adjunct in the treatment of patients with amebic infection and the accompanying chronic colitis, but is not a first-class eradicator

SUMMARY

This case of infection with *Giardia* and the three species of *Councilmania* is interesting, first, because it presents a definite symptomatology. The host to these parasites is ill. There is genuine subjective and objective evidence of it. The clinical behavior is somewhat like that in cases of chronic amebiasis in the temperate zone due to infection with *Endamoeba dysenteriae*. However, it is different qualitatively. There is, apparently, less invasion of the upper digestive tract. There is not a measurable increase in the size of the liver.

The therapeutic behavior has been discussed in the opening paragraphs.

From the patient's point of view, his gain has been in the disappearance of discomfort, increase in muscular and nervous vigor, absence of mental depressions and increased ability to meet the strain of his work. He sums it up by saying that he has not felt so well in at least three years.

From the clinical point of view, the gain has been the receding of a chronic inflammatory condition of the colon.

VARIATIONS IN THE REDUCING POWER (SUGAR) OF NORMAL HUMAN BLOOD ~

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AND
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Although the literature contains numerous determinations of the blood sugar in man, it seems to us that for some reason most of this material is unsatisfactory for the purpose of establishing a norm or reference level. We agree with Gray¹ (1923) that "Standards should be founded not only on a careful examination of a few persons, but on a statistical analysis of many persons." His search of the literature yielded only two series of blood sugar determinations which he considered long enough for statistical treatment, and we find that only few satisfactory series have appeared since his paper was written.

Many of the longer series which have been published are based on hospital material, and although we may be told that the patients were under treatment for conditions which were presumed not to have any effect on the blood sugar, the fact that they were under treatment at all is, in our estimation, sufficient to exclude them from consideration as normal subjects. Determinations made on convalescents are open to the objection that one cannot properly evaluate the effects of prolonged and enforced rest (Riddle and Honeywell,² 1923-1924), a modified or perhaps restricted diet and the medical or surgical treatment previously undergone. Moreover, it would be extremely difficult to duplicate such a series should one desire to test the basis of any conclusions which the authors may have drawn.

Those series which are based on normal men are usually short, and while the subjects may be considered as normal in the sense that they do not have any apparent disease, they often differ widely in age, activity and habits of living. Frequently the subjects and their preparation for the test are not described. In none of the work which has come to our attention is there any attempt to show that the results are truly representative of the general field from which the observations were drawn.

In the present research, attention was directed to the following points:

(1) The establishment with a fair degree of precision of a blood sugar norm, or reference level which presumably could be duplicated in other laboratories.

* From the Department of Physiology, Columbia University.

1 Gray, H. Blood Sugar Standards in Conditions Neither Normal Nor Diabetic. *Arch Int Med* **31** 241 (Feb) 1923.

2 Riddle, O., and Honeywell, H. E. *Am J Physiol* **57** 333, 1923.

(2) Determination of the minimum number of observations necessary to establish a significant series, i.e., a series which would be representative of this general field, within predictable limits

(3) Investigation of the constancy of the blood sugar level in a group of normal persons, a point which has often been stressed in the literature. We wished to test this constancy on uniform material under carefully standardized conditions

(4) Determination of the optimum type of series which would most truly represent the field, e.g., whether for this purpose it is more desirable to make twenty-five observations on one subject or one observation on each of twenty-five subjects

Our subjects were normal, healthy young men and women, students in the medical school, who volunteered for the work, and who were thoroughly familiar with the requirements of the research and the technic involved so far as it concerned them. They came to the laboratory without breakfast and rested comfortably on cots for from twenty to thirty minutes before the taking of the blood sample. At the end of the rest period, a superficial vein in the bend of the elbow was selected and a tourniquet applied to the upper arm, immediately about 2.5 cc. of blood was drawn into a syringe containing a small amount of dry sodium oxalate. With this technic, clotting did not occur. In this connection, it may be observed that a clean, sharp needle of relatively small size (24 gage) makes for quickness and ease in obtaining the sample with a minimum of discomfort to the subject. None of the subjects gave any indication of apprehension, fear or marked discomfort at any time during the period. All the samples were secured between 9 and 10 a.m.

Blood sugar determinations were made in duplicate, the Shaffer-Hartmann³ method (1920-1921) and the conversion table of Duggan and Scott⁴ (1926) being used. All the determinations were made by the same analyst, who was thoroughly familiar with the technic, and variations in the technical results were insignificant in comparison with the physiologic variations.

Our first series consisted of 141 observations, each made on a different person. The mean age of the subjects was 23 years, with a mean deviation of ± 3.4 years, the mean weight (132 subjects only) was 68.5 Kg., with a mean deviation of ± 10.3 Kg. When occasion required that more than one sample be taken from a person, only the initial sample was included in this series, so that the results are comparable in this respect. The raw data are presented in table 1 in the order in which the observations were made.

³ Shaffer, P. A. and Hartmann, A. F. *J. Biol. Chem.* **45** 365, 1920

⁴ Duggan, W. F., and Scott, E. L. *J. Biol. Chem.* **67** 287, 1926

To show that this series actually represents the general field within the limits of precision which we claim, and to determine whether a shorter series would have accomplished the same purpose with a satisfactory degree of precision, these data were submitted to the analytic treatment described by one of us (Scott,⁵ 1927). The series of 141 observations was divided into component series of 5, 10, 20, 28, 35 and 47 observations each. The means (M), mean deviations (ϵ) and the mean deviations of the means (ϵ_M) of these series were then computed, and are presented in their natural order in table 2. The characteristic ϵ_M for each group of series of a given number of observations was then determined by two different methods. In the first method, it was presumed that ϵ for the series of 141 did not differ from ϵ for a series of

TABLE 1—*Raw Data of 141 Blood Sugar Observations made on 141 Medical Students**

| | | | | | | |
|----------------|-----|-----|-----|-----|-----|-----|
| 94 | 94 | 99 | 104 | 96 | 93 | 93 |
| 84 | 102 | 102 | 97 | 115 | 96 | 91 |
| 84 | 102 | 105 | 105 | 116 | 98 | 100 |
| 92 | 94 | 93 | 97 | 102 | 105 | 96 |
| 102 | 94 | 93 | 101 | 97 | 91 | 96 |
| 102 | 94 | 99 | 95 | 98 | 96 | 96 |
| 84 | 102 | 115 | 99 | 104 | 89 | 88 |
| 108 | 92 | 116 | 98 | 96 | 93 | 91 |
| 110 | 94 | 88 | 96 | 92 | 101 | 94 |
| 110 | 99 | 110 | 91 | 102 | 92 | 98 |
| 102 | 89 | 99 | 94 | 89 | 89 | 89 |
| 94 | 99 | 106 | 94 | 87 | 96 | 92 |
| 88 | 97 | 93 | 92 | 97 | 91 | 92 |
| 84 | 107 | 105 | 93 | 94 | 93 | 91 |
| 96 | 102 | 96 | 82 | 102 | 88 | 93 |
| 102 | 102 | 101 | 96 | 97 | 97 | 94 |
| 110 | 102 | 102 | 94 | 96 | 109 | 92 |
| 82 | 105 | 98 | 106 | 92 | 98 | 91 |
| 97 | 99 | 98 | 82 | 89 | 91 | 89 |
| 102 | 98 | 94 | 89 | 102 | 83 | 99 |
| Mean | | | | | | 97 |
| Mean deviation | | | | | | 7.0 |

* The observations are presented in the order in which they were made.

an infinite number of observations by an amount which was physiologically significant. Therefore ϵ for the 141 observations was divided by the square root of the number of observations which was characteristic for the series of each of the groups. The quotients were considered as the "true" ϵ_M 's for series of the respective lengths (table 3, column 4). In the second method, the ϵ_M 's for each group were derived empirically, by considering each M of the group as an original observation and determining ϵ for these means by the formula

$$\epsilon = \sqrt{\frac{\sum d^2}{N-1}}$$

The results are presented in table 3, column 5. It will be seen that in every case the empirical ϵ_M is greater than the "true" ϵ_M by approximately

12 In making predictions, this fact must be taken into consideration. Safe predictions cannot be made with the precision indicated by a strict interpretation of the theory of probabilities, and to make safe prediction with a 95 per cent probability one should add 2.4 to twice the mean deviation of the mean or make other allowance for this discrepancy.

The mean deviations of the mean deviations (ϵ_ϵ) were calculated in a manner similar to that employed for the empirical ϵ_M 's, except that the ϵ 's of each group were now treated as the original observations. The value ϵ_ϵ measures the variation of ϵ in a manner similar to that in which the variability of M is measured by ϵ_M . Before a series can be considered

TABLE 2.—*The Means, Mean Deviations and the Mean Deviations of the Means of The Component Series of the Grand Series of 141 Blood Sugar Observations*

| Group I 28 Series of 5 Each | | | Group II 14 Series of 10 Each | | | Group IV 5 Series of 28 Each | | |
|--------------------------------|------------|--------------|----------------------------------|------------|--------------|---------------------------------|------------|--------------|
| M | ϵ | ϵ_M | M | ϵ | ϵ_M | M | ϵ | ϵ_M |
| 91 | 7.6 | 3.3 | 97 | 10.8 | 3.4 | 96 | 8.4 | 1.6 |
| 102 | 9.5 | 4.2 | 96 | 8.9 | 2.8 | 100 | 6.8 | 1.3 |
| 92 | 7.1 | 3.2 | 96 | 4.1 | 1.3 | 97 | 7.6 | 1.4 |
| 98 | 10.4 | 4.6 | 100 | 5.0 | 1.6 | 95 | 4.9 | 0.9 |
| 97 | 4.3 | 1.9 | 102 | 9.5 | 3.0 | 94 | 4.9 | 0.9 |
| 96 | 4.2 | 1.9 | 99 | 4.4 | 1.4 | | | |
| 98 | 6.7 | 3.0 | 98 | 4.2 | 1.3 | | | |
| 101 | 2.8 | 1.3 | 92 | 6.9 | 2.2 | | | |
| 98 | 5.4 | 2.4 | 102 | 8.0 | 2.5 | | | |
| 106 | 11.9 | 5.3 | 91 | 5.3 | 1.7 | | | |
| 100 | 5.6 | 2.5 | 95 | 4.9 | 1.5 | | | |
| 98 | 3.2 | 1.4 | 94 | 7.1 | 2.2 | | | |
| 100 | 3.9 | 1.7 | 94 | 3.7 | 1.2 | | | |
| 96 | 3.1 | 1.4 | 92 | 2.9 | 0.9 | | | |
| 87 | 6.8 | 3.0 | | | | | | |
| 93 | 8.6 | 3.8 | | | | | | |
| 105 | 9.7 | 4.3 | | | | | | |
| 98 | 4.8 | 2.1 | | | | | | |
| 94 | 6.0 | 2.7 | | | | | | |
| 95 | 5.0 | 2.2 | | | | | | |
| 96 | 5.5 | 2.4 | | | | | | |
| 94 | 4.6 | 2.1 | | | | | | |
| 91 | 3.2 | 1.4 | | | | | | |
| 96 | 9.6 | 4.3 | | | | | | |
| 96 | 3.2 | 1.4 | | | | | | |
| 93 | 4.0 | 1.8 | | | | | | |
| 91 | 1.6 | 0.7 | | | | | | |
| 93 | 3.8 | 1.7 | | | | | | |
| | | | Group III 7 Series of 20 Each | | | Group V 4 Series of 35 Each | | |
| | | | M | ϵ | ϵ_M | M | ϵ | ϵ_M |
| | | | 96 | 8.7 | 1.9 | 97 | 7.9 | 1.3 |
| | | | 98 | 4.3 | 1.0 | 100 | 6.1 | 1.0 |
| | | | 100 | 7.4 | 1.7 | 96 | 7.4 | 1.2 |
| | | | 95 | 6.4 | 1.4 | 94 | 4.7 | 0.8 |
| | | | 98 | 7.6 | 1.7 | | | |
| | | | 94 | 5.7 | 1.5 | | | |
| | | | 93 | 3.4 | 0.8 | | | |
| | | | | | | Group VI 3 Series of 47 Each | | |
| | | | | | | M | ϵ | ϵ_M |
| | | | | | | 98 | 7.6 | 1.1 |
| | | | | | | 98 | 7.6 | 1.1 |
| | | | | | | 94 | 5.0 | 0.7 |

satisfactory, it is necessary that the variability of both M and ϵ be rendered reasonably small, but it is even more important that the variability which remains be reduced to an approximately constant value. The values found for ϵ_ϵ are shown in table 3, column 7. It will be seen that ϵ_ϵ continually diminishes as the number of observations in the series increases, but at a decreasing rate until at about twenty-eight observations the rate of decrease becomes so low that for practical purposes ϵ_ϵ may at this time be considered a constant.

In table 3, column 6, are given the means of the ϵ 's of the respective groups. These will be seen to increase, but also at a decreasing rate as the number of observations becomes greater, until they too become approximately constant at about twenty-eight observations. Thus at

about twenty-eight observations, the range of variation for the first time is covered characteristically (Scott, 1927) This indicates that twenty-eight is the minimum number of observations necessary to establish a significant series

The growth of the series is illustrated in chart 1 Note the tendency of the mean to find its final level and of the hatched area— ϵ —to assume a constant width When these two functions, with reasonable probability, have become sufficiently constant for the purposes of the research, there is no practical point in adding observations Before this, safe prediction cannot be made

When a large number of observations is available, it is possible to test the adequacy of a series by comparing the actual distribution of the observations with that predicted from the mean and the mean deviation of the series to be tested Table 2 shows such great variations of both

TABLE 3—*Analysis of the Variability of the Various Component Series, as Revealed by a Study of the Behavior of the Mean Deviations, Mean Deviations of the Means and the Mean Deviations of the Mean Deviations*

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|-------------------------------------|---|---|---|---|--|
| Number of Observations in the Series N | Number of Series in the Groups n | The Means of the Means ΣM n | Theoretical Mean Deviation of the Means $\frac{7^*}{\sqrt{N}}$ | Empirical Mean Deviation of the Means (See text) | The Mean of the Mean Deviations $\Sigma \epsilon$ n | Empirical Mean Deviation of the Mean Deviation (See text) |
| 5 | 28 | 96 | 3.1 | 4.3 | 5.8 | 2.6 |
| 10 | 14 | 96 | 2.2 | 3.4 | 5.9 | 2.4 |
| 20 | 7 | 96 | 1.6 | 2.7 | 6.2 | 1.9 |
| 28 | 5 | 96 | 1.3 | 2.3 | 6.5 | 1.6 |
| 35 | 4 | 96 | 1.2 | 2.6 | 6.5 | 1.4 |
| 47 | 3 | 97 | 1.0 | 2.3 | 6.7 | 1.5 |

* ϵ for 141 observations

M and ϵ for the series of five and ten observations that it is evident that these series do not permit any precise prediction

The actual 141 observations are compared with the predicted observations on each of the component series which contained more than ten observations (table 4) The first row at the top of the table gives the distribution as predicted from the theory The numbered rows which follow show the actual distribution of the observations about the mean of the indicated series The last three rows of each group show, respectively, the mean distribution for the group, the mean deviation about this mean in absolute units and the mean deviation in percentage of the total number of observations Though there are so few of the longer series in their respective groups that ϵ for their distribution is presumably not yet fixed, it would seem safe to assume on the basis of the table taken as a whole, that safe prediction can be made with a probability of about 95 per cent and to a precision of about 3ϵ when there are twenty-eight

or more observations in the series. It will be noted that when this test is applied to the series from our own laboratory (table 5), and to those of Okey and Robb,⁶ all of the means fall within the predicted limits.

As a result of this analysis, we may conclude that approximately twenty-eight is the minimum number of observations which are necessary before the series may be said to represent the field fairly, and so is the minimum permissible in work with material of this type. It is also the optimum number, for fewer observations would not permit prediction, and it is doubtful whether more would increase the precision sufficiently to justify the added expense of time and effort.

Since twenty-eight constitutes a satisfactory series for the establishment of both M and ϵ , we have in the series of 141 observations a factor of safety of about 400 per cent. Hence it would probably be safe to infer that within the limits of known physiologic significance, the true

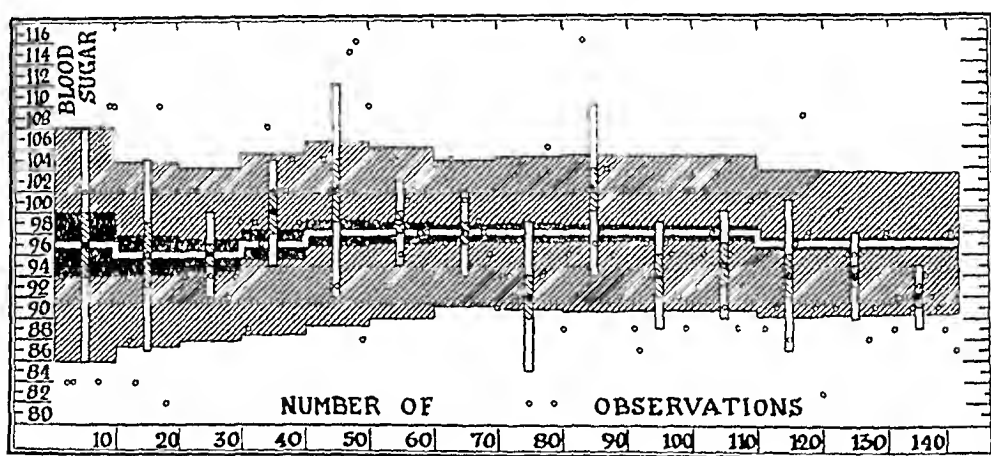


Chart 1—Chart showing the growth and stabilization of the series of 141 blood sugar observations which were made on medical students. The individual determinations are shown in their natural order and are indicated by circles, the means (M) by dots, the mean deviations (ϵ) by outline bars, and the mean deviations of the means (ϵ_v) by hatched bars. The central field shows the characteristics of the cumulative series by increments of 10. The white line indicates the mean, the hatched area the mean deviation and the solid black, the mean deviation of the mean of the growing series.

mean and mean deviation have been established to a precision of three times the mean deviation found. From this it follows that the chances are ninety-five out of 100 that the mean of any series of blood sugar observations made on twenty-eight or more persons under the conditions we have described will not differ by more than three times its mean deviation from 97 mg per hundred cubic centimeters, the mean of our series of 141 observations.

⁶ Okey, R., and Robb, E. I. *J. Biol. Chem.* 45: 165, 1925.

TABLE 4—Fulfillment of Predictions Concerning the 141 Consecutive Observations Made from Each of the Component Series Which Included Twenty or More Observations

| Frequency | | | | | | | | |
|---|----------------|-----------------|-----------------|-----------------|-----|-----|------------|--------------|
| | $\pm \epsilon$ | $\pm 2\epsilon$ | $\pm 3\epsilon$ | $\pm 4\epsilon$ | N | M | ϵ | ϵ_M |
| | Predicted | | | | | | | |
| | 93 | 135 | 140 | 141 | 141 | | | |
| Group III, 20 Observations in Each Series | | | | | | | | |
| 1 | 120 | 137 | 141 | 141 | 141 | 96 | 87 | 19 |
| 2 | 74 | 103 | 129 | 134 | 141 | 98 | 43 | 10 |
| 3 | 85 | 131 | 141 | 141 | 141 | 101 | 74 | 17 |
| 4 | 120 | 137 | 141 | 141 | 141 | 96 | 87 | 19 |
| 5 | 103 | 133 | 141 | 141 | 141 | 98 | 76 | 17 |
| 6 | 91 | 130 | 137 | 141 | 141 | 94 | 57 | 13 |
| 7 | 54 | 93 | 118 | 131 | 141 | 93 | 34 | 08 |
| Mean frequency | 93 | 124 | 135 | 138 | | | | |
| ϵ (absolute) | 25 | 16 | 9 | 4 | | | | |
| ϵ (percentage) | 18 | 11 | 6 | 3 | | | | |
| Group IV, 28 Observations in Each Series | | | | | | | | |
| 1 | 113 | 137 | 141 | 141 | 141 | 96 | 84 | 16 |
| 2 | 92 | 129 | 141 | 141 | 141 | 100 | 68 | 13 |
| 3 | 114 | 137 | 141 | 141 | 141 | 97 | 76 | 15 |
| 4 | 79 | 120 | 137 | 139 | 141 | 95 | 49 | 09 |
| 5 | 86 | 119 | 133 | 137 | 141 | 94 | 49 | 09 |
| Mean frequency | 97 | 128 | 139 | 140 | | | | |
| ϵ (absolute) | 16 | 9 | 7 | 4 | | | | |
| ϵ (percentage) | 11 | 6 | 5 | 3 | | | | |
| Group V, 35 Observations in Each Series | | | | | | | | |
| 1 | 114 | 137 | 141 | 141 | 141 | 97 | 79 | 13 |
| 2 | 83 | 127 | 141 | 141 | 141 | 100 | 61 | 10 |
| 3 | 107 | 137 | 141 | 141 | 141 | 96 | 74 | 12 |
| 4 | 86 | 119 | 137 | 139 | 141 | 94 | 47 | 08 |
| Mean frequency | 92 | 130 | 140 | 140 | | | | |
| ϵ (absolute) | 16 | 9 | 2 | 1 | | | | |
| ϵ (percentage) | 11 | 6 | 1 | 1 | | | | |
| Group VI, 47 Observations in Each Series | | | | | | | | |
| 1 | 103 | 134 | 141 | 141 | 141 | 98 | 76 | 11 |
| 2 | 103 | 134 | 141 | 141 | 141 | 98 | 76 | 11 |
| 3 | 86 | 119 | 133 | 137 | 141 | 94 | 50 | 07 |
| Mean frequency | 100 | 129 | 138 | 140 | | | | |
| ϵ (absolute) | 13 | 9 | 5 | 2 | | | | |
| ϵ (percentage) | 9 | 6 | 4 | 1 | | | | |

TABLE 5—Three Consecutive Observations from Each of Twenty-Five of the 141 Subjects Shown in Order in Columns 1, 2 and 3

| Subject | Observation | | | Subject | Observation | | |
|----------------|-------------|-----|-----|---------|-------------|-----|-----|
| | 1 | 2 | 3 | | 1 | 2 | 3 |
| 1 | 94 | 92 | 92 | 14 | 94 | 94 | 102 |
| 2 | 84 | 96 | 84 | 15 | 102 | 99 | 99 |
| 3 | 84 | 99 | 102 | 16 | 92 | 102 | 102 |
| 4 | 92 | 102 | 102 | 17 | 89 | 102 | 94 |
| 5 | 102 | 110 | 102 | 18 | 99 | 94 | 110 |
| 6 | 110 | 108 | 93 | 19 | 107 | 97 | 94 |
| 7 | 102 | 96 | 99 | 20 | 102 | 87 | 102 |
| 8 | 82 | 94 | 84 | 21 | 102 | 92 | 105 |
| 9 | 102 | 94 | 97 | 22 | 105 | 92 | 99 |
| 10 | 94 | 97 | 105 | 23 | 99 | 93 | 96 |
| 11 | 94 | 97 | 105 | 24 | 92 | 96 | 92 |
| 12 | 102 | 92 | 102 | 25 | 105 | 97 | 82 |
| 13 | 94 | 92 | 94 | | | | |
| Mean | | | | | 97 | 97 | 97 |
| Mean deviation | | | | | \pm 67 | 47 | 61 |

Chart 2 shows not only that the means of such series behave in the manner described, but also that when ϵ_M is calculated from a stabilized ϵ , the means of series as short as five or ten observations fall within these limits. The explanation of this is that the mean is established somewhat earlier than is the mean deviation, so that while it might be possible to predict limits for the true mean from such short series if we had a reliable measure of probability, we are actually unable to do so because the measure of deviation derived from such short series is untrustworthy. Again, with such short series the precision of the mean is so low (chart 2) that predictions made from it would usually have little value.

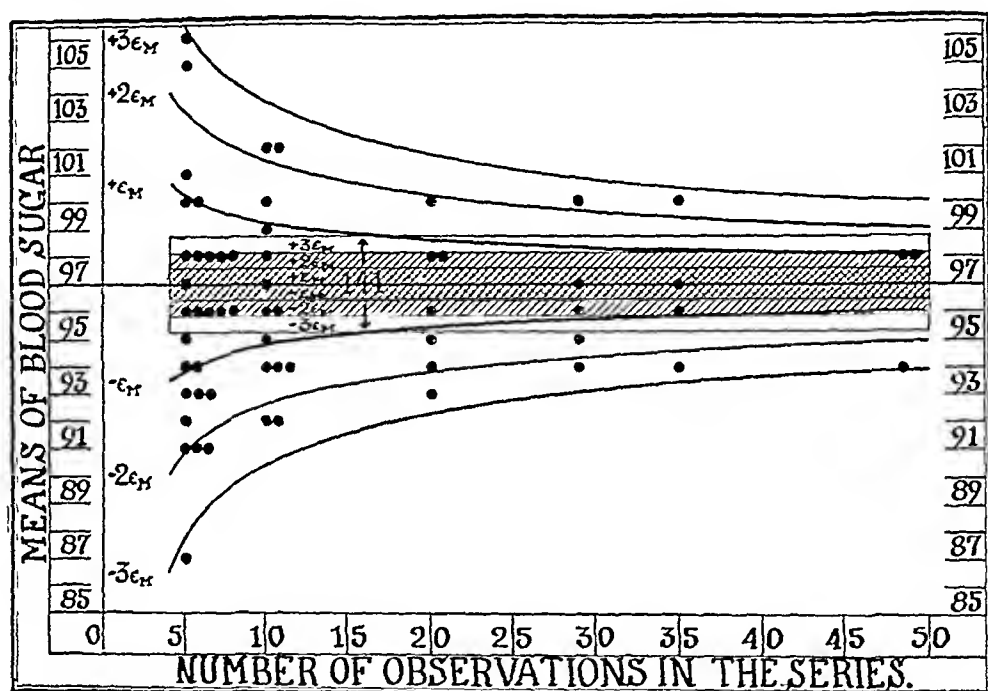


Chart 2—Distribution of the means of the various component series of the series of 141. The parabolic lines represent in order $\pm 1, 2$, and 3 times ϵ_M for the series of the indicated number of observations. ϵ_M was calculated from ϵ for the entire series of 141. The dots represent the means of the component series, the heavy horizontal line that for the grand series. The lighter horizontal lines indicate, in order, $\pm 1, 2$ and 3ϵ for the grand series.

From chart 2 may be read directly the range within which the means of all future series containing five or more observations would be expected to fall, provided that the material and technic were comparable with those we have described.

We were able to make the material still more homogeneous by selecting from the grand series of 141, 120 subjects between the ages of 20 and 25 years, inclusive. In this group the

mean age was 22 ± 1.4 years, the mean weight was 68 ± 9.7 Kg (113 observations) and the mean blood sugar was 96 ± 7.3 mg per hundred cubic centimeters.

Hence it appears that the few persons in the grand series who were out-

side of these limits did not materially influence the results. What would have happened had their numbers been greater we are not in a position to say.

A graphic comparison of our series with some of those already in the literature is presented in chart 3. The observations are grouped in classes of 3 mg. and are plotted on the midvalue of the respective class. Similar observations, then, fall on a line, so that the horizontal distances measure class frequencies while vertical distances measure the amount of sugar found. In chart 4, frequency curves are presented showing the distribution of our observations and its relation to the theoretical distribution curve plotted from the mean and mean deviation of the series of 141. On the same coordinates is also plotted a frequency

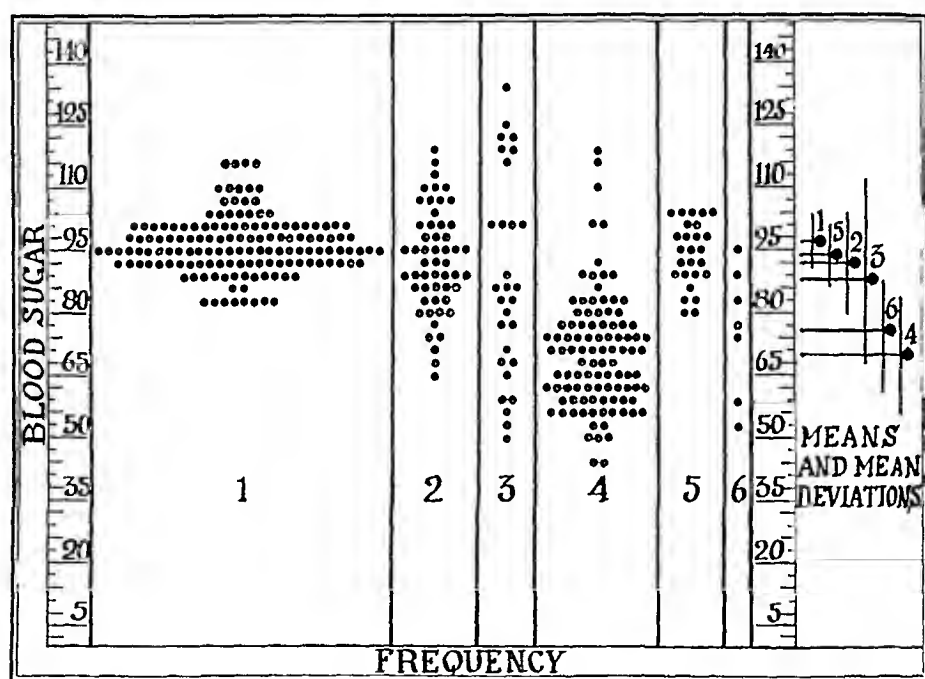


Chart 3—A graphic comparison of various series of blood sugar determinations on man. Each dot represents an observation. The means and mean deviations are plotted at the extreme right of the chart. 1 indicates the 141 observations reported in this paper, 2, fifty-three observations of Goto and Kuno, 1921, 3, twenty-nine observations of Gettler and Baker, 1916, and 4, 100 observations of Cummins and Piness, 1917. The somewhat low mean of this group is possibly related to the effects of hospitalization since the observations were made on convalescent patients. 5 indicates twenty-six observations of Okey and Robb, 1925. While many more than twenty-six observations were reported in these papers, there were but twenty-six subjects, and to make their work comparable with ours only the initial observations are included. 6 indicates seven observations of Strouse, 1920. Here again many more than seven observations were reported, but for one reason or another only seven could be considered comparable with the other groups.

curve constructed from the data assembled by Gray (1923), which he felt included all trustworthy determinations of normal blood sugar on man up to the time of his publication

The satisfactory precision of our series on man as compared with that found for rabbits (Eadie,⁷ 1923, Scott and Ford,⁸ 1923, Clough, Allen and Root,⁹ 1923, Scott, 1927) we attribute to the greater uniformity of the human material and of the conditions which preceded the taking of the sample. It could not have been in the analytic technic, since a research on the normal blood sugar of rabbits conducted by one

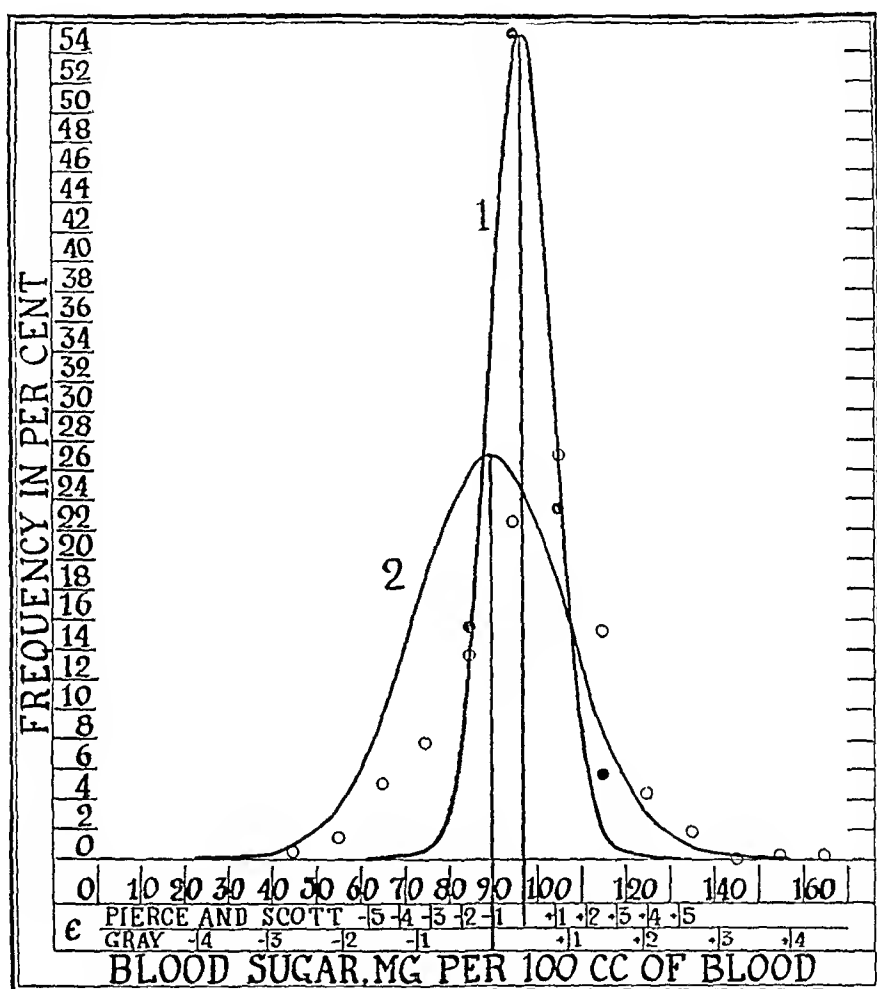


Chart 4—Frequency curves for human blood sugar. Curve 1 is for the series of 141 observations reported in this paper. Curve 2 is for a series of 431 observations collected by Gray, 1923, from various sources. The frequency is plotted in percentage of the total number of observations in the respective series. The lines are the theoretical curves. The dots and circles show the position of the various classes. The dots indicating series 1 and the circles, series 2. Class interval 10, class limits 0 and 9, positions are plotted on midvalues of the respective classes.

⁷ Eadie, G. S. *Am J Physiol* **63** 513, 1923.

⁸ Scott, E. L., and Ford, T. H. *Am J Physiol* **63** 520, 1923.

⁹ Clough, H. D., Allen, R. S., and Root, E. W. *Am J Physiol* **66** 461, 1923.

of us (E L S, so far unpublished) concurrently with this work, employing the same analyst and methods, yielded a mean deviation essentially the same as previously reported for rabbits and about twice that found by us for man

In research work, several methods of establishing the necessary norm are available

- 1 The norm may be established on one set of subjects, and the experimental conditions imposed on a second, presumably similar, set

- 2 The norm may be established on one set of subjects, and at a later date the same subjects may be exposed to the experimental conditions

- 3 The norm may be established on a set of subjects, and the experimental conditions may be imposed immediately on the same subjects

According to the nature of the research (1) A single observation may be made on each of many subjects, (2) many observations may be made on a single subject, and (3) several observations may be made on each of several subjects

Examples of each of these practices may be found in the literature, and the question arises as to which of the methods will yield results of the greatest precision and of the most value in making general predictions. The present research is not sufficiently broad to exemplify all of the foregoing possibilities listed, but it does permit of estimation of certain phases, and, where necessary, will be amplified by data selected from the work of Okey and Robb (1925)

Three or more samples of blood were drawn from each of twenty-five persons of our group of 141 subjects, at intervals of not less than a week. The results of the first three determinations on each of these subjects are shown in table 5. It appears that in spite of the day to day variations which obtain for any given person, the means of the three series of twenty-five are remarkably alike, in this case, they are actually identical. That this similarity is not altogether chance is indicated by table 6, which presents five similar series taken from the work of Okey and Robb. Here, while the means are not all identical, they are so nearly alike that their differences may be considered of no physiologic significance. Thus, so far as generalization based on these series is warranted, the mean basal blood sugar level of a group containing a considerable number of persons may be considered as constant. From table 6, it appears that a group of five is not large enough to give this constant value, while a group of twenty-three is satisfactory. The data are not sufficient to permit determination of the minimum number required for a significant series. Nor can we venture prediction as to the time which may be allowed to elapse between the control and the experimental observations on a given group of persons, although the work indicates that this interval may be at least two weeks. It therefore

follows that the experimental work need not immediately succeed the determination of the norm

Comparison of the series of similar length in table 2 with those of tables 5 and 6 indicates that greater precision may be expected when the same group of persons is used both for the control and for the experiment than when different groups of subjects are employed It would

TABLE 6—Data on Five Consecutive Samples of Blood Taken from Each of Twenty-Three Subjects (from Okey and Robb) *

| | Observation | | | | | M | ε |
|---------|-------------|-----|-----|------|-----|-----------|-----|
| | 1 | 2 | 3 | 4 | 5 | | |
| 1 | 88 | 92 | 93 | 92 | 95 | 92 | 2.6 |
| 2 | 88 | 92 | 102 | 101 | 100 | 96 | 6.6 |
| 3 | 91 | 93 | 95 | 94 | 97 | 94 | 2.2 |
| 4 | 91 | 91 | 91 | 98 | 89 | 92 | 3.5 |
| 5 | 104 | 92 | 87 | 93 | 93 | 94 | 6.2 |
| M | 92 | 92 | 94 | 96 | 94 | for 1st 5 | |
| ε | 6.7 | 0.2 | 5.6 | 3.8 | 6.2 | | |
| 6 | 93 | 102 | 98 | 91 | 89 | 94 | 4.6 |
| 7 | 100 | 102 | 104 | 105 | 94 | 101 | 4.4 |
| 8 | 91 | 104 | 100 | 105 | 96 | 98 | 5.2 |
| 9 | 90 | 102 | 92 | 106 | 104 | 98 | 7.4 |
| 10 | 84 | 94 | 93 | 80 | 89 | 88 | 6.0 |
| M | 92 | 101 | 97 | 96 | 94 | for 2d 5 | |
| ε | 6.7 | 3.9 | 5.0 | 11.2 | 6.2 | | |
| 11 | 107 | 95 | 99 | 98 | 101 | 100 | 4.5 |
| 12 | 96 | 97 | 90 | 96 | 97 | 95 | 3.0 |
| 13 | 89 | 84 | 91 | 92 | 85 | 88 | 3.6 |
| 14 | 79 | 92 | 90 | 85 | 87 | 86 | 5.1 |
| 15 | 98 | 103 | 98 | 84 | 84 | 93 | 8.8 |
| M | 94 | 94 | 94 | 91 | 90 | for 3d 5 | |
| ε | 10.5 | 7.0 | 4.5 | 6.3 | 7.8 | | |
| 16 | 98 | 94 | 92 | 91 | 94 | 94 | 2.7 |
| 17 | 96 | 89 | 91 | 96 | 90 | 92 | 3.4 |
| 18 | 103 | 93 | 87 | 102 | 100 | 97 | 6.8 |
| 19 | 95 | 97 | 93 | 89 | 96 | 94 | 3.2 |
| 20 | 98 | 99 | 102 | 99 | 103 | 100 | 2.2 |
| M | 98 | 94 | 93 | 95 | 96 | for 4th 5 | |
| ε | 6.3 | 3.9 | 5.5 | 6.7 | 5.1 | | |
| 21 | 103 | 98 | 89 | 87 | 89 | 93 | 7.0 |
| 22 | 92 | 103 | 107 | 94 | 105 | 100 | 6.8 |
| 23 | 91 | 89 | 94 | 93 | 99 | 93 | 3.8 |
| Grand M | 94 | 95 | 91 | 94 | 94 | | |
| ε | 6.8 | 5.2 | 5.5 | 6.7 | 6.0 | | |

* In columns 1 to 5 the data appear in their natural order, in columns M and ε the means and mean deviations of the five observations on each individual are given. The series of twenty three were also broken up into component series of five observations each. The means and mean deviations of these component series appear in the appropriate rows. Those for the series of twenty-three, respectively, in the next to the last and the last row.

appear, therefore, that though general predictions are as well justified in one case as in the other, within the limits of precision attained, this precision will be greater when the same subjects are used for both determinations.

The mean of the ε's for twenty-three series of five observations each on single subjects may be calculated from data found in table 6. The result, 4.4, is to be compared with 5.8, column 6 of table 3, in which the

five observations were made on each of five persons. Similarly, the ϵ_M 's are respectively 19 and 26 and the empirical ϵ_M 's, 4 and 43. While, as might be expected, these values indicate somewhat less variability when all of the observations are made on one person, the gain in precision is not impressive, and when the loss in the representative character of the series is considered would lead one to avoid this method of procedure when possible. True, this conclusion is based on short series, but there are a considerable number of such series in each group, so that the conclusion is warranted provisionally, and unless the contrary condition is shown to hold, should be a guide in planning a research. The material at hand is not sufficient to yield a large group of longer series based on single persons, but in table 7 are to be found

TABLE 7—Seven Series of Ten Observations Each

| M, Age 24 | | | C, Age 24 | | F, Age 31 | | | | |
|------------|----|--|-----------|------|-----------|------|------|------|-----------------|
| 1923 | | | 1923 | 1924 | 1924 | 1924 | 1924 | 1924 | 1924 |
| 88 | | | 88 | 109 | 91 | 100 | 100 | 92 | 93 |
| 92 | | | 92 | 101 | 93 | 96 | 94 | 102 | 89 |
| 93 | | | 102 | 97 | 95 | 90 | 93 | 93 | 89 |
| 92 | | | 101 | 99 | 94 | 93 | 94 | 94 | 89 |
| 95 | | | 100 | 98 | 97 | 88 | 99 | 105 | |
| 81 | | | 108 | 97 | 91 | 98 | 100 | 101 | |
| 85 | | | 101 | 97 | 91 | 92 | 95 | 97 | Total |
| 100 | | | 96 | 99 | 98 | 89 | 98 | 89 | 44 obser- |
| 90 | | | 89 | 99 | 99 | 97 | 89 | 94 | vations |
| 90 | | | 90 | 98 | 90 | 87 | 90 | 94 | M, 94 |
| | | | | | | | | | ϵ , 43 |
| M | 91 | | 97 | 99 | 94 | 93 | 95 | 96 | |
| ϵ | 54 | | 68 | 36 | 33 | 45 | 40 | 50 | |

* All data in a given series are derived from a single subject. Since the data of the last four series are all derived from one subject, together with four additional observations we are in possession of a similar series of forty-four observations (From Okey and Robb)

seven groups of ten observations each made on a single person and one of forty-four observations similarly made. These longer series apparently confirm the conclusion just drawn.

In table 8 are to be found four series of twenty-five observations each, in which five observations were made on each of five persons. A comparison of the ϵ 's and of the ϵ_M 's of these series with those of group 4, table 2, does not indicate a significant gain in precision over the series in which each observation was made on a different person. On the other hand, such series must have lost a considerable portion of their value as representatives of the general field from which the observations were drawn.

The conclusion seems to be justified that a series attains value as the number of persons on which the observations are made is increased, the ideal series being one in which the number of observations and the number of persons on which they are made are equal.

SUMMARY

1 The blood sugar of young, healthy men and women under basal conditions may vary between values of about 80 and 115 mg per hundred cubic centimeters of blood. The true mean value probably lies between 95 and 99 mg per hundred cubic centimeters of blood. This statement presupposes that the determinations are made by the Shaffer-Hartmann or the Folin-Wu method (Duggan and Scott,⁴ 1926)

TABLE 8—*Four Series, Each of Twenty-Five Observations, Five Observations Being Made on Each of Five Subjects (from Okey and Robb)*

| Series | | | |
|------------------|-----|-----|-----|
| 1 | 2 | 3 | 4 |
| 88 | 93 | 107 | 98 |
| 92 | 93 | 95 | 94 |
| 93 | 98 | 99 | 92 |
| 92 | 91 | 98 | 91 |
| 95 | 89 | 101 | 94 |
| 88 | 100 | 96 | 96 |
| 92 | 102 | 97 | 89 |
| 102 | 104 | 90 | 91 |
| 101 | 105 | 96 | 96 |
| 100 | 94 | 97 | 90 |
| 91 | 91 | 89 | 103 |
| 93 | 104 | 84 | 93 |
| 95 | 100 | 91 | 87 |
| 94 | 102 | 92 | 102 |
| 97 | 96 | 85 | 100 |
| 91 | 90 | 79 | 95 |
| 91 | 102 | 103 | 97 |
| 91 | 92 | 90 | 93 |
| 98 | 106 | 85 | 89 |
| 89 | 104 | 87 | 96 |
| 104 | 84 | 98 | 98 |
| 92 | 94 | 103 | 99 |
| 87 | 93 | 98 | 102 |
| 93 | 80 | 84 | 99 |
| 93 | 89 | 84 | 103 |
| M 94 | 96 | 98 | 95 |
| ϵ 4.4 | 6.9 | 7.3 | 4.7 |
| ϵ_M 0.9 | 1.4 | 1.5 | 0.9 |

2 The probability is about 95 per cent that the mean of any such series consisting of twenty-five or more observations made on as many persons will not differ more than three times its mean deviation from this true mean

3 Conclusions based on series containing fewer than twenty-five observations are of doubtful significance when the observations pertain to the blood sugar of man. When greater absolute precision is required to support the conclusions than is indicated by $3\epsilon_M$ for twenty-five terms a longer series must be obtained

4 From this it follows that within these limits the mean value of a series of twenty-five or more blood sugar determinations, each of which is made on a different person, may be considered as a constant. Evidence is presented to substantiate this conclusion.

5 A series of observations gains in general significance as the number of subjects on which the observations are made increases, the slightly greater precision which is attained by making many observations on a single person is more than offset by the loss in the representative character of the series.

BACTERIOLOGIC EXAMINATION OF SEVEN HUNDRED AND TWENTY-FOUR SPUTUMS FROM AS MANY PATIENTS WITH BRONCHIAL ASTHMA *

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AND

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BOSTON

During the past ten years we have been interested in the bacteriology of the nonsensitive or asthmatic bronchitis type of asthma, since it is in this type that less is known concerning the cause, furthermore, this type seems to be infectious. Specimens of sputum from 724 patients have been studied during this time. It is during the changeable and cold seasons of the year that the majority of patients suffer from asthmatic bronchitis, therefore, the bacteriologic examinations have been made during the fall, winter and spring of each year since 1918. Consequently, this study was divided into nine periods, namely, the fall, winter and spring of each year since 1918.

Previous to this study, we were accustomed to classify streptococci into three groups, namely, *Streptococcus viridans*, *S. hemolyans* and *S. alpha hemolyans*, but it was soon learned that this classification was not only confusing, but incomplete. It was confusing because the same organism on the same plate would sometimes produce a wide area of hemolysis about several colonies and a narrow area of hemolysis about other colonies, therefore, instead of having two types of organisms, *hemolyans* and *alpha hemolyans*, we had one type of organism producing two grades of hemolysis. The old classification is incomplete in that frequently types of colonies were encountered that produced a brownish pigment or no pigment, therefore, since these colonies were not hemolytic and did not produce a green pigment such as *viridans*, they were not accounted for in the old grouping. Since all types of streptococci either do or do not produce hemolysis, and it is rarely difficult to determine whether there is or is not hemolysis about a colony, we adopted for this work the classification of hemolytic and nonhemolytic streptococci. All colonies were considered as either hemolytic or nonhemolytic, but for completeness the various types of colonies were noted.

Each of these two main groups of streptococci, hemolytic and non-hemolytic, were further subdivided according to Holman's ¹ classification

* From the Laboratory of the Medical Clinic of the Peter Bent Brigham Hospital

¹ Holman, W L. The Classification of Streptococci, J M Research **34** 377, 1916

into eight subgroups according to their ability to ferment the carbohydrates, salicin, mannite and lactose, in times serum waters made according to the method of Hiss²

TECHNIC

Throughout this work the following bacteriologic technic was used. Thick masses of sputum, which was raised during an asthmatic attack or during a severe paroxysm of coughing which usually occurred in the morning, were washed in sterile sodium chloride solution and shaken in 5 cc of plain bouillon. Tubes of melted plain agar to which 0.5 cc. of sterile defibrinated human blood was added were inoculated with varying amounts of the plain bouillon emulsion of sputum, poured into Petri dishes and incubated for thirty-six hours. Various types of colonies were then picked off, subcultivated in dextrose bouillon, and

TABLE 1—*Prevalence and Frequency of Hemolytic and Nonhemolytic Streptococci and of Other Organisms*

| Number of | 1918-1919 | 1919-1920 | 1920-1921 | 1921-1922 | 1922-1923 | 1923-1924 | 1924-1925 | 1925-1926 | 1926-1927 |
|--------------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Sputums examined | 65 | 65 | 56 | 80 | 65 | 101 | 93 | 95 | 104 |
| Hemolytic varieties recovered | 51 | 46 | 49 | 70 | 68 | 21 | 54 | 42 | 110 |
| Hemolytic varieties predominated | 35 | 16 | 4 | 6 | 5 | 2 | 8 | 6 | 21 |
| Hemolytic varieties alone | 1 | 1 | 27 | 12 | 43 | 6 | 5 | 7 | 14 |
| Nonhemolytic varieties recovered | 54 | 51 | 24 | 62 | 26 | 108 | 115 | 93 | 115 |
| Nonhemolytic varieties predominated | 24 | 28 | 2 | 3 | 1 | 2 | 7 | 5 | 30 |
| Nonhemolytic varieties alone | 1 | 13 | 19 | 14 | 11 | 82 | 48 | 35 | 31 |
| Hemolyticus subacidus recovered | 17 | 19 | 0 | 8 | 2 | 2 | 8 | 13 | 42 |
| Hemolyticus anginosus recovered | 13 | 16 | 11 | 29 | 5 | 9 | 18 | 5 | 17 |
| Hemolyticus infrequens recovered | 8 | 3 | 16 | 12 | 28 | 2 | 10 | 11 | 14 |
| Hemolyticus pyogenes recovered | 10 | 7 | 20 | 14 | 26 | 6 | 10 | 4 | 7 |
| Hemolyticus equinus recovered | 1 | 0 | 1 | 2 | 2 | 0 | 2 | 0 | 7 |
| Hemolyticus type I recovered | 2 | 1 | 1 | 4 | 4 | 1 | 5 | 6 | 20 |
| Hemolyticus type II recovered | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 |
| Hemolyticus type III recovered | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 3 |
| Nonhemolyticus ignavus recovered | 16 | 20 | 0 | 5 | 0 | 13 | 12 | 23 | 45 |
| Nonhemolyticus salivarius recovered | 15 | 19 | 5 | 13 | 2 | 18 | 34 | 9 | 18 |
| Nonhemolyticus fecalis recovered | 3 | 5 | 10 | 19 | 9 | 28 | 25 | 29 | 14 |
| Nonhemolyticus mitis recovered | 14 | 7 | 8 | 17 | 10 | 25 | 17 | 4 | 10 |
| Nonhemolyticus equinus recovered | 0 | 0 | 0 | 1 | 0 | 6 | 4 | 4 | 5 |
| Nonhemolyticus type I recovered | 6 | 2 | 1 | 4 | 5 | 12 | 16 | 16 | 17 |
| Nonhemolyticus type II recovered | 0 | 0 | 0 | 0 | 0 | 4 | 1 | 1 | 3 |
| Nonhemolyticus type III recovered | 0 | 0 | 0 | 3 | 0 | 1 | 6 | 2 | 3 |
| Strains of staphylococci recovered | 8 | 16 | 1 | 5 | 5 | 16 | 8 | 4 | 4 |
| Strains of bacilli recovered | 6 | 8 | 5 | 7 | 8 | 1 | 10 | 6 | 10 |
| Strains of other organisms recovered | 5 | 5 | 3 | 0 | 2 | 0 | 0 | 0 | 3 |

incubated for about twenty-four hours. The organisms from this dextrose bouillon growth were stained by Gram's method, and a bile solubility test was made, those organisms which proved to be gram-positive cocci in chains, non-capsulated and bile-insoluble, were inoculated, according to the method of Hiss,² into litmus serum waters which contained salicin, mannite and lactose. These serum waters were incubated for fourteen days unless coagulation took place before that time, and at the end of fourteen days, after the tubes in which change had not taken place were carefully examined to make sure that organisms were present, the organisms were named according to Holman's¹ method of classification.

Table 1 shows for each period already defined the prevalence of hemolytic and nonhemolytic streptococci, also the frequency of each of the subgroups of both of these two types of streptococci and the prevalence of organisms other than

² Hiss, P. H., in Hiss and Zinsser. Textbook of Bacteriology, New York, D. Appleton & Company, 1927.

streptococci Naturally, when various colonies were picked off from plates, many duplicates were picked off and inoculated into the serum waters In the table, however, duplicates are not recorded, only one variety of each organism that was recovered from the same sputum is shown For instance, if two strains of hemolytic *Streptococcus subacidus* were recovered, only one would be recorded, therefore, qualitative rather than quantitative observations are represented

Following the discussion of the observations as recorded in table 1, a few paragraphs are devoted to the results from changes in the original technic The different technic will be described at that time The reason for this change, which was carried on in conjunction with and merely supplemented, the original technic, was to check up on the original technic and either to substantiate or to disprove the observations

During the season 1918-1919, a specimen of sputum was taken and studied from seventy-five patients suffering from asthma Fifty-one strains of hemolytic streptococci were recovered from forty-six of these patients, in thirty-five specimens of sputums this type of organism predominated, and in one specimen no other organism was found These fifty-one strains of hemolytic streptococci were distributed among the following types *infrequens*, eight strains, *anginosus*, thirteen strains, *pyogenes*, ten strains, *hemolyticus* I, two strains, *subacidus*, seventeen strains, and *equinus*, one strain, no strains of *hemolyticus* II and III were recovered Fifty-four strains of nonhemolytic streptococci were recovered from thirty-seven of the patients, in twenty-four of the specimens this type predominated, and once it was found alone These fifty-four strains were distributed as follows *fecalis*, three strains, *nonhemolyticus* I, six strains, *mitis*, fourteen strains, *salivarius*, fifteen strains, and *ignavus*, sixteen strains, no strains of *nonhemolyticus* II and III or of *equinus* were recovered

Organisms, other than streptococci, that were recovered from the sixty-five specimens of sputum were as follows *Staphylococcus pyogenes-aureus*, eight times, *Micrococcus tetragenous*, once, a diphtheroid bacillus, twice, *Bacillus subtilis*, six times, and *Staphylococcus pyogenes-albus*, twice

To summarize these observations, all but three of the fifty-one strains of hemolytic streptococci were included in the four types, *subacidus*, *anginosus*, *pyogenes* and *infrequens* All but three of the fifty-four strains of nonhemolytic streptococci were included in the four following types, namely *ignavus*, *mitis*, *salivarius* and *nonhemolyticus* I The different strains of streptococci were practically equally divided between hemolytic and nonhemolytic but in thirty-five specimens of sputum the hemolytic type of colony predominated, whereas in twenty-four specimens the nonhemolytic type predominated *Staphylococcus pyogenes-aureus* was found eight times and was the only organism other than streptococci that was recovered with any degree of frequency

During the period 1919-1920, sixty-five specimens of sputum from as many persons were studied and streptococci were recovered from fifty-nine of the specimens. Hemolytic streptococci were found in forty-six specimens, in sixteen the hemolytic type predominated, in one, it was the only organism found. The forty-two strains of hemolytic streptococci were distributed as follows: *infrequens*, three strains, *hemolyticus* I, one strain, *pyogenes*, seven strains, *anginosus*, sixteen strains, *subacidus*, nineteen strains, no strains of *hemolyticus* II and III or of *equinus* were recovered.

Nonhemolytic streptococci were recovered from fifty-one specimens, in twenty-eight this type of streptococcus predominated, in thirteen, it was the only organism recovered. The fifty-one strains were grouped as follows: *fecalis*, five strains, *nonhemolyticus* I, two strains, *mitis*, seven strains, *salvarius*, nineteen strains, *ignavus*, twenty strains, no strains of *nonhemolyticus* II and III or of *equinus* were recovered.

Organisms other than streptococci that were recovered from the sixty-five specimens were *Staphylococcus pyogenes-aureus*, sixteen times, *S. pyogenes-albus*, three times, a gram-negative bacillus, eight times, *Micrococcus tetragenous* and *Bacillus subtilis*, one time each.

The observations during this period may be summarized as follows. The nonhemolytic streptococci outnumbered the hemolytic in the proportion of fifty-one of the former to forty-six of the latter, the former predominated in twenty-eight specimens of sputum against the latter in sixteen, and in thirteen specimens the nonhemolytic type was the only organism found, whereas in only one specimen was the hemolytic type found alone. Of the forty-six strains of hemolytic streptococci, all but one were included in the following four types: *infrequens*, *pyogenes*, *anginosus* and *subacidus*. Of the fifty-one strains of nonhemolytic streptococci, all but two were included in the following four types: *mitis*, *ignavus*, *salvarius* and *fecalis*. The only organisms other than streptococci that occurred with any frequency were *Staphylococcus pyogenes-aureus*, sixteen times, and a gram-negative bacillus, eight times.

During the period 1920-1921, fifty-six specimens of sputum were plated. A total of forty-nine strains of hemolytic streptococci were recovered, in twenty-seven specimens, this type of organism was the only one recovered, and in four other specimens it predominated. The forty-nine strains of hemolytic streptococci were divided among the following types: *anginosus*, eleven, *infrequens*, sixteen, *pyogenes*, twenty, *equinus*, one, *hemolyticus* I, one, strains of *subacidus* or of *hemolyticus* II or III were not recovered.

Only twenty-two strains of nonhemolytic streptococci were recovered, in nineteen specimens of sputum it was the only organism recovered and in two other specimens it predominated. The nonhemolytic

streptococci were of the following types *salivarius*, five, *fecalis*, ten, *mitis*, eight, *nonhemolyticus* I, one, no strains of *ignavus*, *equinus* or of *nonhemolyticus* II or III were recovered

The outstanding differences between the results of this period and those of the two former periods which were similar were that twice as many hemolytic types were recovered as nonhemolytic. In about one half of the sputums, hemolytic streptococci were the only organisms found, and in nearly as many specimens, the nonhemolytic type was the only organism recovered, in other words, most of the specimens of sputums grew either type of organism alone, and in only a few were both types found. Another distinct difference was the absence of *hemolyticus subacidus* and *nonhemolyticus ignavus*, both of these organisms were more prevalent than any of the other types in the previous two periods. Other differences were the large proportion of *infrequens*, *pyogenes* and *fecalis*, the decreased frequency of *salivarius* and the fact that staphylococci were recovered only once.

During the period of 1921-1922, eighty specimens of sputum were examined. Seventy strains of hemolytic streptococci were recovered, in twelve specimens of sputum, it was found alone and in six other specimens it predominated. These hemolytic streptococci were of the following types *subacidus*, eight strains, *anginosus*, twenty-nine strains, *infrequens*, twelve strains, *pyogenes*, fourteen strains, *equinus*, two strains, *hemolyticus* I, four strains, and *hemolyticus* III, one strain.

Sixty-two strains of nonhemolytic streptococci were recovered. In fourteen sputums examined it was found alone and in three other specimens it predominated. These nonhemolytic streptococci fell into the following groups *ignavus*, five, *salivarius*, thirteen, *fecalis*, nineteen, *mitis*, seventeen, *equinus*, one, *nonhemolyticus* I and III, four and three, respectively.

The chief differences to be noted in this period were the large numbers of both hemolytic and nonhemolytic organisms recovered, in two thirds of the sputum examined both types of organisms were present in about equal numbers. The types *anginosus* and *fecalis* were present in unusually large numbers, *mitis* was more prevalent than formerly, and in proportion *subacidus* and *ignavus* were recovered less frequently.

During the season 1922-1923, sixty-five specimens of sputum were plated. From these, sixty-eight strains of hemolytic streptococci were recovered, in forty of these specimens examined it was the only organism recovered, and in five others it predominated. The sixty-eight strains were divided among the following *subacidus*, two, *anginosus*, five, *infrequens*, twenty-eight, *pyogenes*, twenty-six, *equinus*, two, *hemolyticus* I, four, and *hemolyticus* II, one.

Only twenty-six strains of nonhemolytic streptococci were recovered, in one specimen of sputum, this organism predominated and in eleven other specimens it was the only organism recovered. The twenty-six strains of nonhemolytic streptococci were as follows: *salvarius*, two, *fecalis*, nine, *mitis*, ten, *nonhemolyticus* I, five.

Therefore, during this season the hemolytic streptococci greatly outnumbered the nonhemolytic streptococci. Of the hemolytic streptococci, all but fourteen strains were either *infrequens* or *pyogenes*, both of which were practically equal in numbers, and together they totaled fifty-six strains. Of the nonhemolytic strains, all but seven were either *fecalis* or *mitis*, and there were nine strains of the former and ten of the latter.

During the season 1923-1924, 101 specimens of sputum were plated. From this large number, only twenty-one strains of hemolytic streptococci were recovered, in two specimens this type of organism predominated and in six others, it was the only organism recovered. These twenty-one strains of hemolytic streptococci were divided among the following types: *subacidus*, two, *anginosus*, nine, *infrequens*, two, *pyogenes*, six, *hemolyticus* I and III, one each.

One hundred and eight strains of nonhemolytic streptococci were recovered, in two specimens of sputum this type of organism predominated, and in eighty-two it was the only organism present. The 108 strains of nonhemolytic streptococci were classified as follows: *ignavus*, thirteen strains, *salvarius*, eighteen, *fecalis*, twenty-eight, *mitis*, twenty-five, *equinus*, five, *nonhemolyticus* I, twelve, II, four, and III, one.

The results of this period were different from those of former seasons. There was a great scarcity of hemolytic streptococci and as great a preponderance of nonhemolytic streptococci. Among the few hemolytic strains, *anginosus*, which was recovered nine times, occurred most frequently and *pyogenes*, isolated six times, was next in frequency, no other hemolytic strains occurred more often than twice. All eight varieties of nonhemolytic streptococci were recovered for the first time, and the following five varieties were recovered often enough to be mentioned as predominating: *ignavus*, *salvarius*, *fecalis*, *mitis* and *nonhemolyticus* I, the latter had not been recovered with any degree of frequency in former periods. *Staphylococcus pyogenes-aureus* was also recovered with the usual frequency.

During the season 1924-1925, ninety-three specimens of sputum were plated. A total of fifty-four strains of hemolytic streptococci were recovered, in eight specimens, this type of organism predominated, and in five others it was the only organism recovered. These fifty-four strains of hemolytic streptococci were the following: *subacidus*, eight, *anginosus*, eighteen, *infrequens*, ten, *pyogenes*, ten, *equinus*, two, *hemolyticus* I, five, and II, one.

One hundred and fifteen strains of nonhemolytic streptococci were recovered, in seven specimens this type of organism predominated and in forty-eight it was the only organism recovered. The 115 strains of nonhemolytic streptococci were the following: *ignavus*, twelve strains, *salvarius*, thirty-four, *fecalis*, twenty-five, *mitis*, seventeen, *equinus*, four, *nonhemolyticus* I, sixteen, and II and III one and six, respectively.

In this period, the hemolytic streptococci were recovered in the average frequency of former periods and, as usual, *anginosus*, *infrequens* and *pyogenes* were most often encountered, and *anginosus* was more prevalent than in some years. Nonhemolytic streptococci, however, were recovered more frequently than in the past, and the same varieties that were most prevalent in the previous period were again most frequently encountered during this period, there were *equinus*, *salvarius*, *fecalis*, *mitis* and *nonhemolyticus* I, and these were recovered a similar number of times as formerly, with the exception of *salvarius* which was recovered twice as frequently as in any former year.

During the season 1925-1926, ninety-five specimens of sputums were examined. From these, forty-two strains of hemolytic streptococci were recovered, in seven specimens, it was the only organism found and in six others it predominated. The following hemolytic strains were recovered: *subacidus*, thirteen, *anginosus*, five, *infrequens*, eleven, *pyogenes*, four, *hemolyticus* I, six, *hemolyticus* II and III, one and two, respectively.

A total of ninety-three strains of nonhemolytic streptococci were recovered, this type of organism predominated in five specimens of sputum, and it was the only organism recovered in thirty-five specimens. The nonhemolytic strains were as follows: *anginosus*, twenty-eight, *salvarius*, nine, *fecalis*, twenty-nine, *mitis*, four, *equinus*, four, *nonhemolyticus*, I, sixteen, *nonhemolyticus* II and III, one and two, respectively.

The observations of this period resembled those of the former period as to the prevalence of both hemolytic and nonhemolytic streptococci in the sputums that were cultured, but the prevalence of the different strains of these two types of streptococci varied as follows. Of the hemolytic strains, *subacidus* was more prevalent and *anginosus* and *pyogenes* were distinctly less prevalent than usual. Among the nonhemolytic types, *ignavus* was more prevalent than usual, and *mitis* and *salvarius* were much less prevalent than usual. During this period, the majority of the hemolytic strains were *subacidus* and *infrequens* and the majority of the nonhemolytic strains were *ignavus*, *fecalis* and *nonhemolyticus* I.

During the season 1926-1927, 104 specimens of sputum were plated. One hundred and ten strains of hemolytic streptococci were recovered,

it was the only organism found in fourteen of the specimens examined, and it predominated in twenty-one. These hemolytic strains were the following: *subacidus*, forty-two, *anginosus*, seventeen, *infrequens*, fourteen, *pyogenes*, seven, *equinus*, seven, *hemolyticus* I, twenty, *hemolyticus* II and III, two and three, respectively.

One hundred and fifteen strains of nonhemolytic streptococci were recovered, in thirty specimens of sputum this organism predominated and in thirty-one other specimens it was the only organism recovered. These nonhemolytic strains were the following: *ignavus*, forty-five, *salivarius*, eighteen, *fecalis*, fourteen, *mitis*, ten, *equinus*, five, *nonhemolyticus* I, seventeen, and *nonhemolyticus* II and III, three each.

During this period, hemolytic streptococci were recovered more frequently than formerly, and nonhemolytic streptococci were recovered with about the same frequency as during the past four periods. Of the hemolytic strains, *subacidus*, *hemolyticus* I and *equinus* were more frequent than formerly, *pyogenes* was recovered less frequently, *anginosus* and *infrequens* were found with the usual frequency. Among the nonhemolytic streptococci, *ignavus* was much more prevalent than formerly and *mitis* was less prevalent than usual, *salivarius*, *fecalis* and *nonhemolyticus* I were recovered in nearly the same numbers as usual. Another unusual observation this season was that more varieties than usual were prevalent in large numbers, and the nonhemolytic included five varieties, whereas formerly two or three varieties usually comprised the greater number of organisms.

In table 1, the variation in the occurrence of the different varieties of streptococci that were prevalent during the different periods is evident. It is not shown, however, whether there is any variation during each period. A careful study of each period does not reveal any distinct variation for that period, in other words, practically the same varieties of streptococci that were prevalent during the fall months continued to be similarly prevalent during the succeeding winter and spring months. Therefore, whatever variation occurred during the periods studied was brought about by the intervening summer months. In other words, the same varieties of streptococci prevailed throughout the successive cool months of each year, but the intervening warm summer period often altered considerably the prevailing streptococci so that in the next successive fall, winter and spring different varieties of streptococci from those of the preceding fall, winter and spring prevailed.

Another point not brought out in the table, but which may be of interest, is a discussion regarding the number of different varieties of streptococci that were recovered from the same sputum. In 43 per cent of the specimens of sputum examined, only one variety of streptococcus was recovered, in 34 per cent, two different varieties were recovered, in

16 per cent, three different varieties were found, in 4 per cent, four varieties and in 1 per cent, five varieties were recovered. Therefore, from a third of the specimens only two different varieties of streptococci were recovered and from less than a third of the specimens more than two different varieties. When more than one different strain of streptococcus was recovered from the same sputum, all strains were sometimes of the hemolytic type, sometimes of the nonhemolytic type, often both types were represented. In other words, one specimen might contain any combination of the sixteen different varieties of streptococci, although usually a total of five different varieties was not exceeded, but in a third of the sputums examined there was a combination of only two different varieties, and in less than a third of the specimens the combination consisted of more than two different varieties.

VARIATIONS IN TECHNIC

During the periods of 1918-1919 and 1919-1920, in addition to the technic already described, the majority of the organisms were carried through further subcultures. The organisms from the dextrose bouillon growth which was cultured from individual colonies on blood agar plates were again plated on blood agar and grown for twenty-four hours. From these second plates, different colonies were again fished and inoculated into dextrose bouillon and incubated for twenty-four hours. From these bouillon cultures, the litmus serum waters containing the three carbohydrates were inoculated as previously described. This second plating made it certain that the organism which was inoculated into serum waters was in pure culture, whereas only one plating, the usual number throughout this work, might leave one in doubt as to the purity of the organisms that were inoculated into the carbohydrate serum waters.

The results as judged by the serum water fermentation tests were identical with both methods for all of those organisms that survived the second plating, therefore, it is fair to assume that one plating resulted either in a pure culture, or, if not, the contamination was too slight to influence the fermentation test. At any rate, one plating when done with care is satisfactory. It was found that the second plating was unsatisfactory, because so many organisms that were hemolytic in the first place either failed to grow or lost their hemolytic property in the second plate.

During the season 1920-1921, it was noted that from the first twenty-five specimens of sputum plated nearly always only one type of streptococcus, either hemolytic or nonhemolytic, was recovered, and that it was rare to recover both types from the same sputum. This was different from the results of the two former seasons and was rather disturbing. Therefore, in addition to the usual method of plating, the

following technic was used, so that two different specimens of the same sputum were plated. Some of the washed sputum was grown in dextrose bouillon over night, and from this culture blood agar plates were inoculated and incubated for thirty-six hours. From these plates various colonies were picked, macerated in small quantities of dextrose bouillon and then inoculated into the Hiss litmus serum water containing the three carbohydrates. Thirty specimens were cultured in this manner, and in twenty-seven the results, as judged by the fermentation of the serum waters, were identical for both methods of plating, the same forty-two strains of the various types were identical for both methods. In three specimens, there were the following differences: in one sputum, only *pyogenes* was recovered by the original method, whereas both *pyogenes* and *anginosus* were recovered by the second method; in another sputum, *pyogenes* and *subacidus* were recovered by the original method but only *pyogenes* by the second method; in the third sputum, *pyogenes* and *infrequens* were recovered by the original method, but in addition to these, *mitis* was also recovered by the second method. Therefore, in these three specimens there were identical observations with four strains and different observations with three strains. Since in the forty-nine strains recovered from the thirty specimens there were only three variations, and in the thirty sputums there was only one material change, namely, one was changed from purely hemolytic to both hemolytic and nonhemolytic, it is evident that the observations already reported as made by the original method of plating must be accurate for practical purposes.

During the study, duplicates of colonies with similar morphologic characteristics were picked off and inoculated into dextrose bouillon and then into the serum waters, but frequently, since all colonies proved to contain the same organism, only one variety of either the hemolytic or nonhemolytic type was recovered. Since, as already described, the method of plating was not at fault, it was felt that possibly an insufficient number of colonies were being picked from the original plates with the result that some strains were being missed. Therefore, beginning in the period 1922-1923, and continuing throughout the remaining periods, many more colonies were picked from the plates. Several colonies of each of those having different morphologic characteristics were picked off, the phrase "different morphologic characteristics of the colonies" will be discussed later. By picking off these colonies, however, it was learned that rarely was a variety of organism missed when fewer colonies were picked off, and when a large number of colonies were picked off, only a larger number of duplicates were obtained. For example, if a plate contained only colonies of nonhemolytic streptococci, when two dark green colonies were picked off and cultured in the carbohydrate serum waters, both turned out to be *salivarius*, when four colonies were

similarly selected, all four would be the same. For another example, two colonies of a narrow hemolytic and two of a wide hemolytic character might be selected. The two narrow hemolytic colonies might be, for example, *pyogenes*, and the two wide hemolytic colonies might be, for instance, *subacidus*. When four of the narrow and four of the wide hemolytic colonies were selected, the result would be the same, namely, four strains of *pyogenes* and four of *subacidus*. If great care is exercised in determining the morphologic characteristics of the colonies and duplicate colonies of each different type are picked off, there is only a slight chance of missing some variety of streptococcus.

Early in the period 1923-1924, it was noted that few hemolytic colonies and a great preponderance of nonhemolytic colonies were being obtained, also that the nonhemolytic colonies were much out of the usual proportion. As it was thought that possibly thirty-six hours was not a sufficient time to allow some colonies to produce hemolysis, a duplicate plate was permitted to incubate for forty-eight hours and sometimes longer, but this added length of incubation did not increase the number of hemolytic colonies, nor did any nonhemolytic colonies become hemolytic. Therefore, there was a real preponderance of nonhemolytic streptococci. It might be well to state at this point that incubation of plates for only twenty-four hours is liable to result in the missing of hemolytic colonies, that is, some colonies that are minute and do not show hemolysis after twenty or twenty-four hours' growth will by thirty-six hours become larger and show definite hemolysis.

MORPHOLOGY

During this work, four distinct types of hemolytic colony of streptococci were evident. They were a pinpoint colorless colony surrounded by a narrow zone of hemolysis, a pinhead colony, sometimes white, sometimes brownish, surrounded by a zone of hemolysis about as broad as the diameter of the colony, a pinpoint or pinhead colony surrounded by a wide zone of hemolysis, and a green colony surrounded by a narrow zone of hemolysis. The latter type of colony was not observed frequently, but the three former types were usual. The various strains of hemolytic streptococci, however, did not show strict adherence to any one type of colony, in fact, the type of colony for the different strains varied among the three usually described to such a degree that no inference could be drawn from the appearance of the colony as to the type of organism it contained. In the same plate, for example, *subacidus* would produce both a wide and a narrow zone of hemolysis and the size of the colonies would be both pinpoint and pinhead. Although usually the large colonies showed the wide zone of hemolysis, in the same plate a small colony with a wide zone of hemolysis and a large colony with a narrow

zone of hemolysis would be noted. Therefore, the importance of picking off all of the different types of colonies for study is evident, although in so doing several duplicates of the same organism will result, and, as already shown, more than three different varieties of streptococci in the same specimen of sputum is unusual, the usual number is only one or two different varieties.

Three types of nonhemolytic streptococci were noted. A green colony was most frequently encountered, a brown colony was almost as frequently noted, and a white colony was occasionally noted. All of the eight varieties of nonhemolytic streptococci, however, developed into any of these three types of colony and not infrequently the same type of organism would produce two types of colony on the same plate. Therefore, the pigment of the nonhemolytic colony, as Holman¹ found, cannot be taken as a criterion of the strain of the streptococcus present.

The morphology of the organisms themselves also varied. The same organism might be present from one colony as a long chain and from another in a short chain on the same plate. The same organism would be large cocci in chains in one colony and small diplococci in chains in another colony, both colonies being from the same plate. For example, from the same plate *anginosus* was described in the two following ways: wide hemolysis containing long chains of large cocci and narrow hemolysis containing short chains of diplococci. The length of the chain and the size of the individual coccus were not criterions as to the type of the organism.

CONCLUSIONS

From the bacteriologic examination of 724 washed specimens of sputum from the bronchial tubes of as many patients with asthmatic bronchitis the following facts are evident:

The prevalence of hemolytic and nonhemolytic streptococci varies from year to year, but it does not seem to vary during the cool period of the same year; changes in prevalence occur during the summer season.

The presence of the subgroups or individual varieties of both hemolytic and nonhemolytic streptococci varies in the same manner. One year a certain organism may not be present at all (*ignavus*, 1922-1923), and another year it may represent nearly half of all the strains of that particular type (*ignavus* 1926-1927). Such wide variations are, however, unusual.

Among the hemolytic varieties of streptococci, not more than four of the eight were predominant during any one period, and among the nonhemolytic varieties of streptococci, not more than five of the eight predominated during any one period, usually a lesser number of varieties were predominant.

In any one specimen of sputum, it was unusual to recover more than three different varieties of streptococci, in one third of the specimens, only two varieties were recovered, and in more than one third of the specimens, only one variety of streptococcus was recovered.

The morphology of the colony or of the organism is not a criterion as to the particular organism, litmus serum waters containing salicin, mannite and lactose (Holman's method) separate the individual organism.

With the exception of *Staphylococcus pyogenes-aureus*, which occasionally is present in notable numbers, bacteria other than streptococci are not prevalent in the sputum of asthmatic patients in sufficient numbers to be comparable to the streptococcus group.

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Book Reviews

ENDOKRINE KRANKHEITEN VON PROF DR HANS CURSCHMANN, Direktor der Medizinischen Universitätsklinik zu Rostock I M Mit einem Beitrag von Dr Med et Phil Franz Prange, M D, Assistent der Medizinischen Universitätsklinik zu Rostock I M Paper Price, 850 marks Pp 151, with 48 illustrations and index Leipzig Theodor Steinkopff, 1927

Dr Curschmann has written the chapters on the thyroid, parathyroid, the hypophysis and the suprarenals, and Dr Prange has written the chapter or section on diseases of the ovaries and testis. The authors succeeded best in the description and classification of the syndromes related to hyperactivity and hypoactivity on the various endocrine glands. They were more unfortunate in the theoretical part of the work. There is a brief introduction of less than five pages which contains an amazing assortment of dogmatic assertions, theories and questionable facts, as shown by the following quotations:

"It seems to be established that none of the hormones partake of the chemical nature of proteins." We have rather clear evidence that the thyroid hormone as it leaves the thyroid gland is a protein or at least in combination with the protein thyroglobulin.

The following statement is certainly questionable: "Disturbances due to malfunction of single endocrine glands (monoglandular disturbances) are never seen, all endocrine disturbances are of pluriglandular origin." The author states further that "hormones act on the entire metabolism, on the nervous system, and especially on the vegetative nervous system."

"We know that hormones act especially on the sympathetic and parasympathetic systems." "There is no question that the entire endocrine system is under the control of the central nervous system (zerebralen Zentren)."

The author compares this cerebral center (hypothetically located in the mesencephalon) to the keyboard of a piano. It need not be pointed out that this conception of the delicate control of all the endocrine glands through cerebral activity is entirely hypothetical, and yet the author states it as a proved fact.

The thymus gland is included, without question, among the endocrines, although the evidence for such function on the part of this gland is questionable. And, finally, the author classes choline as the hormone of gastro-intestinal motility, a theory which is questionable.

In the sections dealing with the specific endocrine malfunctions when the authors are closer to their own practical experience, they display more evident respect for facts and more critical judgment. Nevertheless, we find such statements as the following, speaking of spasmophilia in children: "There is no doubt that hypofunction of the parathyroids plays a rôle in infantile convulsions or spasmophilia."

Such ex cathedra teaching does not establish the facts and hinders rather than helps the solution of the problem. There is no chapter on the pancreas, insulin and diabetes. The illustrations in the book are on the whole well chosen and classic, but the monograph as a whole cannot be considered a significant contribution to medical science or to medical practice.

IODINE COMPOUNDS

THEIR SELECTIVE ABSORPTION BY THE HYPERPLASTIC THYROID GLAND OF THE DOG^{*}

H B VAN DYKE, M D
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Marine and Feiss¹ and Marine and Rogoff² have demonstrated both by perfusion of the surviving isolated organ and by injections in vivo that the thyroid gland is able to remove iodide iodine from circulating fluids with extreme rapidity. Apparently no one, however, has studied iodine in other forms which are sometimes believed to behave characteristically when administered to persons suffering from disorders of the thyroid gland. The experiments reported in this paper have therefore been undertaken to learn, if possible, to what extent compounds containing iodine other than iodide iodine are selectively absorbed by the thyroid gland.

TECHNIC

In all of the experiments, the selective absorption of the various iodine compounds by the dog's hyperplastic thyroid gland was determined in vivo. When the preliminary experiments were performed about three years ago,³ a large proportion of the animals had suitable goiters. In attempting to complete the work recently, I had great difficulty in finding goitrous dogs, probably because of the present extensive use of iodized salt which both dog and man ingest. Frequently, therefore, as in the experiment, the results of which are shown in table 4, a control piece of thyroid tissue was removed aseptically and its iodine concentration was determined before the experiment was performed. The difference in iodine concentration between the right and left lobes before the injection of an iodine compound was always much less than that which was considered significant in the experiments. Although most of the animals were under ether anesthesia during experimentation, similar results were obtained when narcosis was produced by barbital. If the glands were of sufficient size, control

^{*} From the Department of Physiological Chemistry and Pharmacology, The University of Chicago.

1 Marine, David, and Feiss, H O. The Absorption of Potassium Iodide by Perfused Thyroid Glands and Some Factors Modifying It, *J Pharmacol & Exper Therap* 7 577, 1915.

2 Marine, David, and Rogoff, J M. The Absorption of Potassium Iodide by the Thyroid Gland In Vivo Following its Intravenous Injection in Constant Amounts, *J Pharmacol & Exper Therap* 8 439, 1916.

3 van Dyke, H B. On the Absorption by the Hyperplastic Thyroid Gland of Various Forms of Iodine Introduced Intravenously, *J Pharmacol & Exper Therap* 25 166 1925.

samples were taken from the lowest part of each lobe. An iodine compound such as thyroxine was then injected intravenously. After a suitable time, a second sample consisting of the middle part of each lobe was removed. Thereupon potassium iodide solution was given intravenously, some minutes later, the remaining superior portions of the lobes were resected. The second and third samples were always incised before removal to make sure that the circulation, grossly judged by bleeding, was adequate.

In the preliminary experiments, iodide iodine appeared to be the most rapidly absorbed. Hence it was used as a means of comparing the absorption of the iodine of the particular compound being examined with that of the iodine of potassium iodide. The iodine determinations in thyroid tissue were made by Kendall's method.⁴ In the case of inorganic iodine dissolved in isotonic saline solution, the determination was made by direct titration with standardized two-hundredth normal sodium thiosulphate solution. Often mention is made of specimens of thyroid which did not contain iodine, what is meant is that iodine could not be detected by Kendall's method. The tables illustrate typical results from twenty-six successful experiments.

THE SELECTIVE ABSORPTION OF IODINE IODINE

In seven experiments, small amounts of iodine dissolved in isotonic saline solution were administered intravenously, and the changes in the

TABLE 1—*The Selective Absorption of Iodine Iodine and of Iodide Iodine*

| Time, Minutes | Lobe | Ether anesthesia Weight of Dried Thyroid Gland Analyzed, Mg | Mongrel of 70 Kg weight Iodine in Dried Thyroid Gland, per Cent | Comment |
|------------------|------|---|---|--|
| | | | | |
| 0 | R | 48.2 | 0 | Control |
| 5 | | | | 10.0 mg of iodine iodine in isotonic saline solution injected intravenously |
| 20 | L | 95.5 | 0 | |
| | L | 120.9 | 0 | |
| 25 | | | | 5.6 mg of iodine as potassium iodide injected intravenously |
| 30 | R | 71.2 | 0.007 | Amounts too small to be titrated accu- rately |
| | R | 84.2 | 0.012 | |

iodine concentration of the thyroid gland were determined. The experiment the results of which are given in table 1 is typical of what was found when the interval between injection and removal of samples was less than forty-five minutes. Iodine seemed not to be taken up by the gland. In some of the experiments in which the injection was made one to two hours before samples were resected, the iodine concentrations of the glands were definitely increased. However, the hyperplastic thyroid gland did not take up iodine iodine at the remarkably rapid rate at which it removes iodide iodine from the blood stream.

Probably free iodine is bound chiefly by the blood lipoids when it is injected intravenously. A certain amount may slowly be reduced to iodide iodine which is then removed from the circulating fluids by

⁴ Kendall, E. C. Determination of Iodine in Connection with Studies in Thyroid Activity. *J. Biol. Chem.* 43:149, 1920.

the thyroid Free iodine in comparison with iodide iodine, even if one assumes that the former is absorbed, seems therefore to have little significance in thyroid physiology if experiments such as these are used as a criterion

THE SELECTIVE ABSORPTION OF IODATE IODINE

Iodate iodine appeared to be taken up by hyperplastic glands much more quickly than iodine iodine Ten experiments including control observations, were performed because of the smaller difference between the selective absorption of iodate iodine and that of iodide iodine Table 2 contains data from an experiment in which only iodate iodine

TABLE 2—*The Selective Absorption of Iodate Iodine*

| Time, Minutes | Lobe | ether anesthesia | Mongrel of 8.5 Kg weight | | Comment |
|------------------|------|---|--|--|--|
| | | Weight of Dried Thyroid Gland Analyzed, Mg | Iodine in Dried Thyroid Gland, per Cent | | |
| 0 | L. | 130.1 | 0 | | |
| 6 | R. | 281.9 | 0 | | |
| 7 | | | | | 9.95 mg iodine as potassium iodate injected intravenously |
| 18 | L. | 264.6 | 0.036 | | |
| 20.5 | R. | 170.3 | 0.019 | | |
| 32 | L. | 180.1 | 0.038 | | |
| 32 | R. | 148.6 | 0.038 | | |

TABLE 3—*The Selective Absorption of Iodate Iodine and of Iodide Iodine*

| Time, Minutes | Lobe | ether anesthesia | Mongrel of 10 Kg weight | | Comment |
|------------------|------|---|--|--|--|
| | | Weight of Dried Thyroid Gland Analyzed, Mg | Iodine in Dried Thyroid Gland, per Cent | | |
| 0 | L. | 87.9 | 0.023 | | Control |
| 7 | R. | 179.4 | 0.032 | | |
| 12 | | | | | 10.7 mg iodine as potassium iodate injected intravenously |
| 22 | L. | 162.4 | 0.048 | | |
| 24.5 | R. | 218.4 | 0.053 | | |
| 25 | | | | | 5.44 mg iodine as potassium iodide injected intravenously |
| 38 | L. | 127.9 | 0.064 | | |
| 38 | R. | 179.7 | 0.072 | | |

was administered After about eleven or twelve minutes, there was a marked change in the iodine content of the gland (The smaller value of the sample from the right lobe removed at 20.5 minutes probably was due to interference with the circulation by the ligation of the vessels of the lower pole on that side) During the succeeding ten to fifteen minutes, there was little change in the amount of iodine contained in the thyroid

An example of the second type of experiment is to be found in the experiment the data of which are given in table 3 Before injections, the iodine concentration of the gland was higher than in the first experiment It is well known that the lower the initial concentration of

iodine in the thyroid, the greater is the ability of the gland to absorb selectively iodide iodine. In the second experiment, one would expect a *proportionally* less iodate and less iodide iodine to be taken up than in the experiment of table 2. There was a definite selective absorption of both iodate and iodide iodine. From other experiments and from those the data of which is presented, there appeared to be a greater increase in the final concentration of iodine after the injection of iodide than one would encounter if iodate instead of iodide iodine had been given on the second occasion. It should be noted that only about half as much iodide iodine was usually administered.

Some idea of the rate at which iodide iodine was taken up by such a hyperplastic gland may be gained from an examination of table 4, in the experiment of which thyroxine iodine was first injected. Usually ten minutes after the administration of about 5 mg. of iodide iodine into a suitable animal, there was an increase in the concentration of iodine in the thyroid gland equal to that following the administration of twice as much iodate iodine at a somewhat longer period previously.

THE SELECTIVE ABSORPTION OF THYROXINE IODINE

As is generally known, the administration of thyroxine to an animal characteristically increases the basal metabolic rate after a prolonged latent period. Just how this occurs is not known, but it seemed possible that some light might be thrown on the mechanism of the action of thyroxine by ascertaining whether or not the hormone, so far as it can be identified by its iodine, is acutely taken up by the hyperplastic thyroid gland which selectively absorbs iodate and especially iodide iodine. Thyroxine made by Kendall's method⁵ and by the later process of Harington⁶ was used in four experiments, all of which gave identical results. From one to two hours after the injection of thyroxine, it was possible to detect only untitratable traces of iodine in the samples of thyroid analyzed. However, there was a well marked acute increase in iodine concentration in samples of thyroid removed from the same animal a much shorter time after the injection of a considerably smaller amount of iodide iodine. These results are illustrated in the data of table 4. The thyroxine used in this experiment had been made by Harington's method.

Whether or not such observations have any significance as to the pharmacologic action of thyroxine remains unsettled. Too little time elapsed between injection of the thyroxine and analysis of the thyroid for the characteristic effect on metabolism to have appeared.

⁵ Kendall, E. C. Isolation of the Iodine Compound Which Occurs in the Thyroid, *J. Biol. Chem.* **39** 125, 1919. Purchased from E. R. Squibb and Sons Company.

⁶ Harington, C. R. Isolation of Thyroxine from the Thyroid Gland, *Biochem. J.* **20** 293, 1926. Purchased from The British Drug Houses, Ltd.

THE SELECTIVE ABSORPTION OF IODINE COMPOUNDS AFTER
BILATERAL LIGATION OF THE SUPRARENAL GLANDS

Some years ago, Marine and Baumann⁷ reported that there appeared to be a definite relationship between the thyroid gland and the suprarenal cortex in the maintenance of the normal metabolism of the rabbit. Resection of the main suprarenal bodies usually resulted in an increased production of heat which failed to appear if the animals had previously been thyroidectomized. Marine and Baumann were of the opinion that in the rabbit there was little interference with the storage of iodine of the thyroid glands of animals that had been subjected to bilateral suprarenalectomy alone. At about the same time, Black, Hupper and Rogers⁸ published data from which they concluded that the feeding of suprarenal

TABLE 4—*The Selective Absorption of Thyroxine Iodine and of Iodide Iodine*

| Time | | Father anesthesia Young fox terrier mongrel of 8.0 Kg. weight | | | Comment |
|------|-----|--|---|--|--|
| Hr | Min | Lobe | Weight of Dried Thyroid Gland Analyzed, Mg | Iodine in Dried Thyroid Gland, per Cent | |
| | | R | 153.9 | 0 | Sample removed aseptically day preceding experiment |
| 0 | | L | 44.0 | 0 | Additional control |
| 0 | 3 | | | | 13.2 mg. of iodine as thyroxine (20.25 mg.) dissolved in 4.5 cc. of tenth normal sodium hydroxide injected intravenously |
| 1 | 31 | R | 122.9 | Trace | |
| 1 | 33 | L | 69.0 | Faint trace | |
| 1 | 35 | L | 147.9 | Trace | |
| 1 | 39 | | | | 4.88 mg. of iodine as potassium iodide injected intravenously |
| 2 | 5 | L | 149.1 | 0.047 | |
| | | L | 145.6 | 0.062 | |
| | | R | 213.5 | 0.047 | |

"residue" to dogs was accompanied by an increase in content of iodine of the thyroid. There thus was a possibility of this interrelationship being further manifested by an alteration in the ability of the hyperplastic thyroid gland of the dog to take up iodine after resection of the suprarenal glands.

In five successful experiments, the suprarenal glands were either removed or ligated. The completeness of the operation was confirmed

7 Marine, David, and Baumann, Emil J. Influence of Glands with Internal Secretions on the Respiratory Exchange. III. Effect of Suprarenal Insufficiency (by Removal) in Thyroidectomized Rabbits, *Am J Physiol* **59** 353 (Feb) 1922. V. Effect of Suprarenal Insufficiency (by Removal) in Thyroidectomized Rabbits, *J Metab Research* **1** 777 (June) 1922, VI. Further Data on the Effect of Suprarenal Insufficiency (by Removal) in Rabbits, *J Metab Research* **2** 1 (July) 1922.

8 Black, E. M., Hupper, Marjorie and Rogers, John. The Effects of Adrenal Feeding on the Iodine Content of the Thyroid Gland. *Am J Physiol* **59** 222 (Feb) 1922.

by necropsy in each case. After from six to seven hours, further thyroid samples were removed and an iodine compound was injected intravenously immediately afterward. Analysis of the final samples revealed to what extent iodine was selectively bound by the thyroid gland under such conditions.

The experiment of table 5 indicates more clearly how the data were obtained. After suprarenal resection, as far as the thyroid gland was concerned, there did not seem to be any change in either the iodine content or in the ability of the gland selectively to absorb iodide iodine. In other experiments, iodine and iodate iodines were taken up by hyperplastic thyroid glands exactly as in normal animals. It is obvious, of course, that the results might have been different had I injected the iodine compounds at a considerably later period when symptoms of insufficiency of cortical "secretion" would have been manifest.

TABLE 5—*The Selective Absorption of Iodide Iodine after Bilateral Ligation of the Adrenal Glands*

| Time | | Lobe | Ether anesthesia | Mongrel of 10 kg weight | Comment |
|------|-----|------|---|--|--|
| Hr | Min | | Weight of Dried Thyroid Gland Analyzed, Mg | Iodine in Dried Thyroid Gland, per Cent | |
| 0 | 18 | | | | Right suprarenal gland ligated |
| 0 | 32 | | | | Left suprarenal gland ligated |
| 0 | 57 | L | 440.8 | 0.022 | Control |
| | | L | 313.4 | 0.026 | |
| | | L | 466.6 | 0.020 | |
| 6 | 36 | L | 472.5 | 0.021 | 15.3 mg iodine as potassium iodide injected intravenously |
| | | L | 344.6 | 0.021 | |
| 6 | 45 | | | | |
| 7 | 5 | R | 414.0 | 0.056 | |
| | | R | 322.2 | 0.052 | |

COMMENT

The results of most of the experiments which have been performed in an attempt to determine the manner in which iodine is removed from the gastro-intestinal tract have led to the conclusion that if iodine iodine is administered, it is found to have been reduced to iodide in serum.⁹ Moreover, Marine and Rogoff¹⁰ pointed out that eight hours after the injection of an iodide solution into an animal having a well marked hyperplasia of the thyroid gland, pharmacologic evidences of an altered secretion appeared. These facts, together with the results of the experiments cited in this paper, suggest that in practice iodide iodine is of chief

⁹ Sollmann, Torald. The Fate of Iodine, Iodides, and Iodates in the Body, *J. Pharmacol. & Exper. Therap.* **9** 269, 1917.

¹⁰ Marine, David, and Rogoff, J. M. How Rapidly Does the Intact Thyroid Gland Elaborate its Specific Iodine-Containing Hormone? *J. Pharmacol. & Exper. Therap.* **9** 1, 1916.

pharmacologic significance in altering thyroid secretion. There appears to be little experimental basis for the use of free iodine, even if loosely linked with iodides, as in Lugol's solution, in the treatment of patients with various types of goiter.

As far as the experiments reported in this paper are concerned, the reason for the slight absorption of iodine iodine and especially of thyroxine iodine perhaps is that these substances were more or less selectively taken up by other tissues in the body. Some idea of the correctness of such a view could be furnished by estimations of the iodine content of the blood coincidently with the removal of samples of thyroid and of other organs.

SUMMARY

1. An attempt has been made by acute experiments to determine quantitatively the rates at which the hyperplastic thyroid gland of the dog selectively absorbs various iodine compounds. Thyroxine iodine is very slowly taken up, while free iodine is absorbed relatively more rapidly. Iodate iodine is bound quickly by such glands but apparently not so quickly as iodide iodine, which is selectively absorbed by the hyperplastic gland more rapidly than any of the iodine compounds studied.

2. The selective absorption of iodine, iodate and iodide iodines is unaffected by complete bilateral ligation of the suprarenal glands six or seven hours previously.

Following intravenous administration there was a decrease from the lowest control pulse rate, within the first five minutes, of from 8 to 42 per cent or an average decrease of 24 per cent. This was generally followed by an increase, the average in this group being an increase of 24 per cent, while subsequent pulse rates varied usually only slightly from the control rate.

Fifteen minutes after the subcutaneous injection there was a decrease in the pulse rate of 13 per cent with limits from $+9$ to -39 per cent. Later, the average pulse rate was near the control rate although still below at the end of thirty and sixty minutes, and above at the end of two hours.

No appreciable change took place in the pulse rate in those experiments in which ephedrine was given orally.

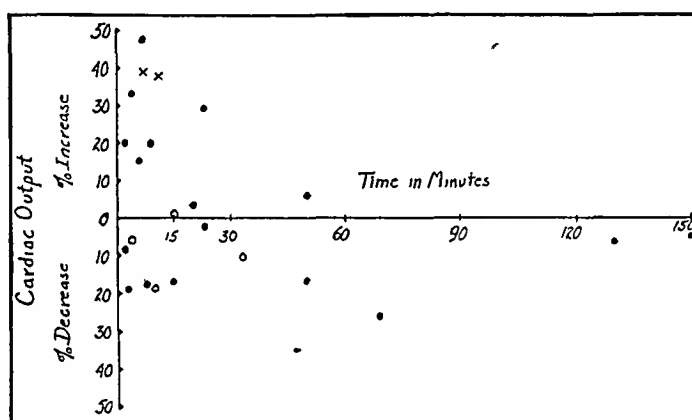


Chart 1—The effect of ephedrine on the minute cardiac output of normal dogs at various time intervals after intravenous injection, circle indicates 0.5 mg per kilogram, black dot, 1 mg per kilogram, x, 4 mg per kilogram.

Blood Gases—When the animals were breathing oxygen blood samples naturally showed an increase in the arterial oxygen content. The experiments in which the blood samples were drawn immediately before or from three to five minutes after the oxygen consumption was determined, showed in each case after the administration of ephedrine an increase in the arterial oxygen content from 1 to 2.5 volumes per cent. This change was not evident during the final determinations when the blood flow approached the control level. The changes in the venous oxygen content generally led to a diminution of the arteriovenous difference.

Oxygen Consumption—An increase in the oxygen consumption lasting from fifteen to thirty minutes was noted in every experiment following intravenous injection. The degree of increase varied considerably in individual experiments. After the subcutaneous administration the oxygen consumption increased more than 10 per cent in five

TABLE 1—The Effect of Ephedrine Intravenously on the Pulse Rate, Oxygen Consumption and Minute Cardiac Output

| Experiment | Weight Kg | Before Ephedrine | | | Dose Mg per Kg | Time After Adminis- tration, Pulse Rate Minutes per Minute | After Ephedrine | | Percentage Change | | |
|-----------------|--------------|--------------------------|---|------------------------------------|-------------------|---|---|------------------------------------|-----------------------|----------------|-------|
| | | Pulse Rate per Minute | Oxygen Consump- tion per Minute Cc | Cardiac Output per Minute Cc | | | Oxygen Consump- tion per Minute Cc | Cardiac Output per Minute Cc | Oxygen Consumption | Cardiac Output | |
| | | | | | | | | | | | |
| L ₁ | 11.3 | 88 | 97.1 | 2,000 | 0.5 | 4 | 76 | 151.7 | 1,890 | +55 | -55 |
| | | | | | | 10 | 102 | 118.4 | 1,630 | +21.4 | -18.5 |
| | | | | | | 15 | 96 | 99.9 | 2,010 | +2.2 | +0.5 |
| V ₅₀ | | | | | | 33 | 116 | 99.0 | 1,800 | +2.2 | -10 |
| I ₂ | 13.6 | 111 | 107.8 | 1,645 | 1 | 2 | 66 | 151.4 | 1,700 | +13 | -8.8 |
| | | | | | | 6 | 64 | 122.8 | 1,900 | +14 | +15.5 |
| | | | | | | 23 | 112 | 119.0 | 2,130 | +10.3 | +29.5 |
| V ₇₁ | | | | | | 130 | 100 | 107.3 | 1,560 | -0.6 | -5.2 |
| L ₄ | 8 | 100 | 69.9 | 1,810 | 1 | 4 | 92 | 92.0 | 2,450 | +31.5 | +33.1 |
| | | | | | | 7 | 162 | 92.0 | 2,720 | +31.5 | +47.8 |
| | | | | | | 22 | 72 | 99.4 | 1,910 | +42.0 | +3.8 |
| V ₁ | . | | | | | 50 | 64 | 73.6 | 1,540 | +5.0 | -16.2 |
| | | | | | | 150 | 148 | 70.8 | 1,750 | -1.2 | -5.0 |
| L ₅ | 11 | 70 | 98.9 | 2,485 | 1 | 3 | 60 | 123.3 | 2,020 | +34.5 | -18.7 |
| | | | | | | 9 | 84 | 147.2 | 2,980 | +49.0 | +20.0 |
| | | | | | | 23 | 80 | 161.9 | 2,180 | +63.5 | -1.0 |
| V ₇₃ | | | | | | 50 | 72 | 139.8 | 2,680 | +41.0 | +6.3 |
| I ₆ | 12 | 92 | 114.7 | 2,500 | 1 | 2 | 64 | 131.0 | 3,010 | +14.0 | +20.5 |
| | | | | | | 8 | 96 | 182.0 | 2,060 | +58.8 | -17.6 |
| | | | | | | 15 | 96 | 136.5 | 2,090 | +19.0 | -16.1 |
| | | | | | | 47 | 132 | 118.3 | 1,640 | +3.2 | -31.4 |
| V ₇₀ | | | | | | 69 | 108 | 106.5 | 1,850 | -7.2 | -26.0 |
| | | | | | | 20 hrs | 140 | 87.7 | 1,870 | -23.5 | -25.2 |
| I ₁ | 14.8 | 120 | 113.2 | 2,070 | 1 | 7 | 88 | 150.1 | 2,840 | +4.8 | +37.2 |
| V ₇₁ | | | | | | 11 | 112 | 161 | 2,835 | +12.1 | +38 |

experiments in the first fifteen minutes, while in one there was only a slight change from the control. Of these increases of more than 10 per cent, one lasted thirty minutes and another was still over 10 per cent at the end of two hours. In those experiments in which a stomach tube was passed, there was a decrease in the consumption of oxygen within fifteen minutes in two dogs and a slight increase in one, while subsequent determinations proved to be variable.

Cardiac Output—1 **Ephedrine Given Intravenously** Immediately following the injection there was a decrease in the minute cardiac output in three experiments averaging 11 per cent, while in the other three experiments there was an average increase of 26.9 per cent. After thirty minutes the output had returned to normal limits. Chart 1 shows the results of all the intravenous experiments. One dog ($V_{56} E_3$, see also E_r) reacted to the injection with a pronounced decrease in the minute

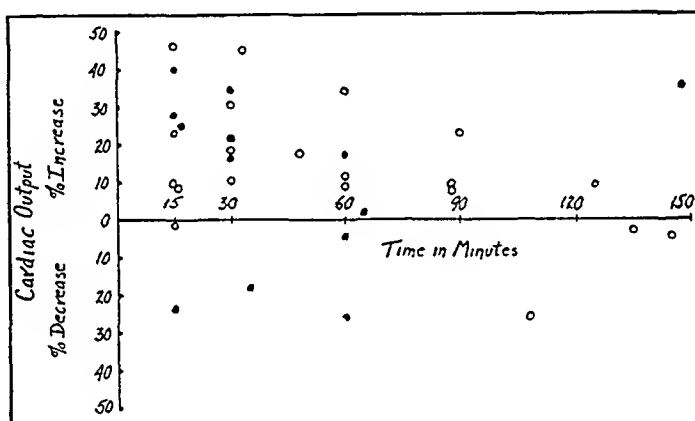


Chart 2—The effect of ephedrine on the minute cardiac output of normal dogs at various time intervals after subcutaneous injection, black dot indicates 1 mg per kilogram, circle, 2 mg per kilogram

output, and a half hour later still had not returned to the normal control level. This dog was also used in studying epinephrine hydrochloride and was found to react with a decrease in the minute cardiac output. The question of idiosyncrasy to these drugs suggests itself as an explanation.

2 **Ephedrine Given Subcutaneously** Regardless of the dose, in five experiments there was an average increase in the minute output of 32.6 per cent within fifteen minutes, while in one there was a decrease of 23.5 per cent and in three the result was within the limit of error allowed, —10 per cent (chart 2). After thirty minutes there was an average increase of 25.3 per cent in seven determinations and a decrease of 18 per cent in one. There was a return to normal in five experiments at the end of sixty minutes, in two the time required was from 120 to 145 minutes, and in two others the return to a normal flow was not studied.

TABLE 2—*The Effect of Ephedrine Subcutaneously on the Pulse Rate, Oxygen Consumption and Minute Cardiac Output*

| Experiment | Weight kg | Before Ephedrine | | | Dose Mg per Kg | Time After Adminis- tration, Pulse Rate Minutes per Minute | After Ephedrine | | Percentage Change | | |
|-----------------|--------------|--------------------------|---|------------------------------------|-------------------|---|-----------------------|----------------|-------------------|-------|-------|
| | | Pulse Rate per Minute | Oxygen Consump- tion per Minute Cc | Cardiac Output per Minute Cc | | | Oxygen Consumption | Cardiac Output | | | |
| F ₇ | 14.5 | 88 | 140.6 | 2,580 | 1 | 15 | 96 | 157.2 | 3,310 | +11.7 | +28.3 |
| V ₅₃ | | | | | | 30 | 88 | 114.3 | 3,000 | +2.6 | +16.3 |
| I ₈ | 8.6 | 120 | 99.9 | 2,660 | 1 | 60 | 96 | 140.6 | 2,470 | 0 | -1.2 |
| V ₇₁ | | | | | | 15 | 100 | 94.1 | 2,110 | -5.1 | -23.5 |
| I ₉ | 10.5 | 112 | 89.2 | 2,500 | 1 | 30 | 84 | 94.1 | 3,240 | -5.1 | +21.7 |
| V ₇₀ | | | | | | 60 | 80 | 92.5 | 1,970 | -7.2 | -26.0 |
| F ₁₀ | 9.3 | 72 | 79.1 | 2,310 | 1 | 17 | 88 | 81.0 | 3,120 | -9.0 | 124.8 |
| V ₇₃ | | | | | | 35 | 100 | 92.9 | 2,050 | +1.0 | -18.0 |
| F ₁₆ | 16 | 60 | 117.1 | 2,300 | 2 | 65 | 84 | 93.7 | 2,540 | +7.2 | +1.6 |
| V ₇₅ | | | | | | 15 | 60 | 108.6 | 3,240 | +37.0 | +40.2 |
| E ₁₂ | 20 | 96 | 111.0 | 1,800 | 2 | 30 | 64 | 97.5 | 3,110 | +23.0 | +31.6 |
| V ₇₇ | | | | | | 60 | 64 | 72.5 | 2,710 | -8.2 | +17.3 |
| F ₁₃ | 13.2 | 66 | 91.9 | 2,220 | 2 | 15 | 64 | 116.4 | 3,370 | +25.0 | +46.5 |
| V ₅₁ | | | | | | 30 | 81 | 153.7 | 2,720 | +31.2 | +18.2 |
| | | | | | | 60 | 72 | 139.1 | 3,090 | +18.8 | +34.1 |
| | | | | | | 90 | 84 | 132.7 | 2,830 | +13.3 | +23.0 |
| | | | | | | 115 | 76 | 129.0 | 2,200 | +10.1 | -1.1 |
| | | | | | | 16 | 72 | 162.0 | 5,190 | +12.5 | +8.3 |
| | | | | | | 18 | 64 | 176.5 | 5,650 | +22.5 | +17.9 |
| | | | | | | 88 | 88 | 142.2 | 5,160* | -1.1 | +7.5 |
| | | | | | | 108 | 88 | 162.0 | 3,530 | +12.5 | -26.0 |
| | | | | | | 15 | 72 | 99.0 | 2,240 | +1.2 | +9.0 |
| | | | | | | 33 | 78 | 101.1 | 3,230 | +10.0 | +15.0 |
| | | | | | | 60 | 72 | 86.1 | 2,480 | -8.8 | +11.6 |
| | | | | | | 88 | 72 | 100.8 | 2,400 | +6.0 | +8.1 |
| | | | | | | 148 | 68 | 100.8 | 3,000 | +35.1 | +35.1 |
| | | | | | | 208 | 61 | 99.0 | 2,010 | +1.2 | -9.1 |
| F ₁₄ | 7.7 | 80 | 70.2 | 2,010 | 2 | 15 | 76 | 77.1 | 2,480 | +10.0 | +23.3 |
| V ₅₁ | | | | | | 30 | 121 | 75.6 | 2,630 | +7.8 | +30.8 |
| L ₁₅ | 10.7 | 92 | 90.7 | 2,480 | 2 | 125 | 100 | 68.1 | 2,190 | -2.5 | +9.0 |
| V ₇₀ | | | | | | 15 | 60 | 102.3 | 2,440 | +13.0 | -1.6 |
| | | | | | | 30 | 80 | 98.6 | 2,710 | +8.9 | +10.5 |
| | | | | | | 60 | 80 | 100.1 | 2,700 | +10.2 | +8.9 |
| | | | | | | 135 | 84 | 93.0 | 2,100† | +2.5 | -3.2 |

* Arterial oxygen content assumed to be the same as in preceding determination

† Blood samples did not check average taken for calculation

3 Ephedrine Given Orally Fifteen minutes after administration there was an increase in the circulatory minute volume of 18.3 per cent in one experiment and no change in another (chart 3). Three determinations made at the end of thirty minutes showed an average increase of 20 per cent in the output of the heart. In 120 minutes the cardiac output had returned to normal. As there are only three experiments in this group conclusions drawn from them must be guarded. Although the change in the minute output was greater in two experiments than it was in any by the intravenous or subcutaneous method and the average of the three oral experiments stands well above the other averages, we only wish this to be considered as a suggestive observation.

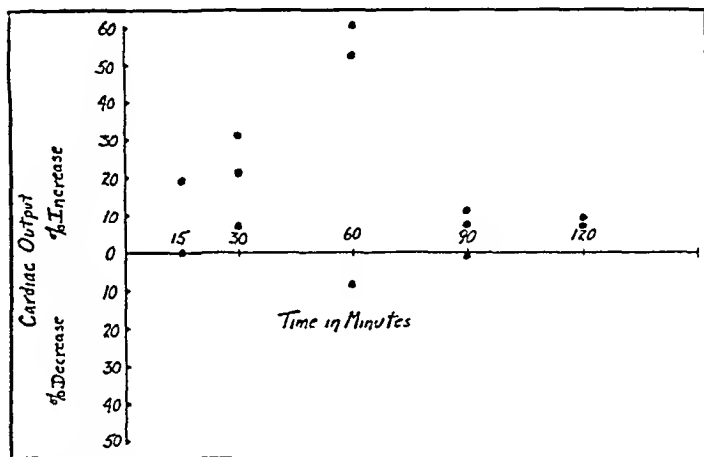


Chart 3—The effect of ephedrine on the minute cardiac output of dogs at various time intervals after oral administration

COMMENT

From the foregoing data it is evident that the minute cardiac output of normal dogs generally increases in response to ephedrine given intravenously, subcutaneously or by mouth in therapeutic doses. In a comparison of charts 1, 2 and 3, it is noted that the increase in cardiac output develops most rapidly following the intravenous administration of ephedrine, second most rapidly after the subcutaneous injection, and least rapidly when the drug is given orally. This, of course, is to be expected. The duration of the action is about equal for the subcutaneous and oral method of administration. Chart 4 is made by averaging the results of all experiments and plotting the results against time intervals. While the number of experiments does not allow such mean values to be an exact representation of the effect of the drug it does give a rough indication of the degree and duration of action.

The problem of clinical importance is concerned with the use of ephedrine in acute circulatory insufficiency, commonly called shock. A

TABLE 3—The Effect of Ephedrine Orally on the Pulse Rate, Oxygen Consumption and Minute Cardiac Output

| Inpatient | Weight kg | Before Ephedrine | | | Dose Mg per kg | Time After Adminis- tration, Pulse Rate Minutes per Minute | After Ephedrine | | Percentage Change | |
|-----------|--------------|--------------------------|---|------------------------------------|-------------------|---|---|------------------------------------|-----------------------|----------------|
| | | Pulse Rate per Minute | Oxygen Consump- tion per Minute Cc | Cardiac Output per Minute Cc | | | Oxygen Consump- tion per Minute Cc | Cardiac Output per Minute Cc | Oxygen Consumption | Cardiac Output |
| | | | | | | | | | | |
| I 10 | 11 | 80 | 121.3 | 2,170 | 3 | 30 | 101.2 | 3,210 | -16.3 | +31.2 |
| V 11 | | | | | | 60 | 104.2 | 3,970 | -11.2 | +60.7 |
| | | | | | | 90 | 107.6 | 2,890 | -11.1 | +11.0 |
| | | | | | | 120 | 103.6 | 2,700 | -11.6 | +9.3 |
| I 14 | 8.9 | 60 | 101.8 | 2,095 | 3 | 15 | 87.8 | 2,500 | -12.2 | +19.3 |
| | | | | | | 30 | 95.2 | 2,270 | -1.8 | +7.1 |
| | | | | | | 60 | 121.1 | 3,020 | +22.1 | +22.8 |
| V 11 | | | | | | 90 | 93.3 | 2,260 | -8.1 | +7.5 |
| | | | | | | 120 | 102.5 | 2,210 | +0.7 | +7.3 |
| | | | | | | 15 | 100.6 | 2,890 | +3.6 | 0 |
| I 10 | 11 | 104 | 97.0 | 2,830 | 3 | 30 | 117.1 | 3,510 | +20.8 | +21.1 |
| | | | | | | 60 | 97.0 | 2,670 | 0 | -8.3 |
| | | | | | | 90 | 101.3 | 2,870 | +7.6 | -0.7 |

drug, to be of most use in combating this emergency, must fulfill certain requirements, namely, it must increase the circulatory minute volume an appreciable amount and maintain this increase for an appreciable length of time without any depressing after effects, cause a maintained increase of the blood pressure, and decrease the pulse rate

Chen⁶ has reported good results following the use of ephedrine in experimental shock, satisfying the preceding requirements, provided the degree of shock is not too severe. He believes, as do we, that the results are accomplished by direct action on the heart muscle. Blalock² has arrived at the same conclusions in mild hemorrhagic shock, with the exception of the slowing of the pulse rate. In severe shock, ephedrine, according to Blalock, has less beneficial effects and may be injurious. The effect of ephedrine on the pulse rate in anesthetized dogs was not studied by us, but Chen has shown that in this state there is an acceleration in the rate

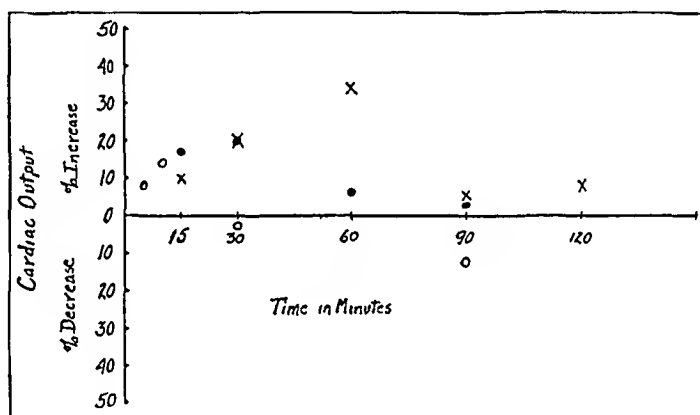


Chart 4—The average change in minute cardiac output at various time intervals after the administration of ephedrine by three different methods—intravenous, subcutaneous and oral, circle indicates intravenous, black dot, subcutaneous, \times , oral

We encountered but one instance in this series which would lead us to say that ephedrine was a dangerous drug, and in this experiment we were using a far smaller amount than that given by Chen⁷ as the minimal lethal dose for dogs intravenously, which is from 70 to 75 mg per kilogram. We did not follow this observation with more experiments and the doses used in other instances did not lead us to believe that there was any great danger in the administration of ephedrine in small amounts.

Chen and Meek⁴ have shown that ephedrine diminishes the size of the spleen. Such an action would afford an explanation of the increase in the oxygen content of the arterial blood, in as much as it would cause

6 Chen, K. K. *J. Pharmacol. & Exper. Therap.* **26** 83, 1925

7 Chen, K. K. *J. Pharmacol. & Exper. Therap.* **27** 61, 1926

an increase in the number of circulating red blood corpuscles and, therefore, in the oxygen carrying capacity of the blood. That this is a function of the spleen has been maintained by Barcroft for a number of years. Lamson⁸ is not in accord with this idea, having concluded from a number of experiments concerned with the effect of epinephrine hydrochloride on the red blood count that the liver, or the portal circulation, is the seat of the series of events which leads to the temporary polycythemia.

It would seem, from an examination of the tables, that the increases in the oxygen consumption had a decided bearing on the values obtained for the cardiac output. The fact that this does not always occur is important, and also that we had a large number of experiments in which the oxygen consumption varied considerably during the control periods but the arteriovenous oxygen difference compensated in these, giving determinations on the circulatory minute volume which were in agreement.

Our results using epinephrine hydrochloride are reported in a preceding paper. In a comparison of the dosage used and the consistency and duration of action of epinephrine hydrochloride and ephedrine the following points are noted. The dose of epinephrine hydrochloride used corresponds to a large therapeutic dose for an adult patient, while the amount of ephedrine given is probably the average amount that would be given to a patient. Intravenously, epinephrine hydrochloride increases the circulatory minute volume more consistently than ephedrine, whereas the duration of action is about one third as long, the ratio being five minutes for epinephrine hydrochloride to fifteen minutes for ephedrine. Subcutaneously, ephedrine and epinephrine hydrochloride in the doses used have practically the same effect on the cardiac output, as regards consistency, degree and duration of action. Ephedrine usually causes a slowing of the pulse rate of normal dogs, while epinephrine hydrochloride usually has the opposite effect.

Because of this and because the action of ephedrine is less variable, and furthermore because secondary depression following the initial increase in cardiac output occurs more frequently when epinephrine hydrochloride is used, we believe that ephedrine is the better drug of the two in the treatment of circulatory collapse.

SUMMARY

Ephedrine given intravenously to normal dogs usually causes an immediate increase in the minute cardiac output, which lasts fifteen minutes or longer. If the drug is given subcutaneously the action is more uniform and of a greater degree, developing within fifteen minutes and

⁸ Lamson, P. D. *J. Pharmacol. & Exper. Therap.* 9:129, 1916.

lasting forty-five minutes or longer. If it is given orally an increase develops after thirty minutes and lasts about an hour.

In normal dogs the pulse rate is slowed after the intravenous and subcutaneous administration of ephedrine.

The subcutaneous method of administration of ephedrine for its effect on the circulatory mechanism is probably the most suitable, although the oral method gave the highest average in the few experiments performed.

CONCLUSIONS

Ephedrine increases the minute cardiac output, and the results of its use in shock indicate that it is of value as a cardiac stimulant.

DUODENAL ULCER

OBSERVATIONS ON THE BEHAVIOR OF STOMACH AND DUODENUM IN THE PRESENCE OF PAIN *

MALCOLM J WILSON, M D

TORONTO

Various hypotheses have been advanced in explanation of the pain in duodenal ulcer. This pain has been ascribed to irritation of exposed nerve endings in the ulcer base by the acid gastric juice, or to sensitization of the pain-producing mechanism in some way by acid. Bonninger,¹ Palmer² and others hold such views. Mechanical irritation by coarse particles of food is the cause assigned by Pick³. Spasm of the pyloric sphincter or of the duodenal cap has been put forward by Glaessner and Kreuzfuchs⁴ and many others. Tension, due to an inhibition of relaxation of the pyloric sphincter, combined with strong gastric peristalsis, has been advanced by Hurst⁵ as the cause. That distention of the stomach is an important element in the pain of gastric ulcer and that this pain is readily relieved by passing a tube into the stomach is stated by Poulton⁶. That the pain is possibly due to movement of the pylorus toward the midline, "thus putting traction on the duodenum," has been suggested by Alexis Thomson⁷. Again, it is conceivable that the pain might result from an exaggeration of the normal hunger contractions, and indeed, the term "hunger pains" is frequently employed in this connection by both patients and physicians.⁸ Finally, it is possible that spasm elsewhere than at the pyloric sphincter can cause pain, as in a case described by Reynolds and McClure.⁹

* Thesis submitted for Degree of Doctor of Medicine, University of Toronto. The results of this investigation were presented at the meeting of the American Gastro-Enterological Association, Atlantic City, N. J., May 2, 1927.

† From the Department of Medicine, University of Toronto, and the Medical Service of the Toronto General Hospital.

1 Bonninger, M. *Berl klin Wchnschr* **45** 396, 1908.

2 Palmer, W. L. *Mechanism of Pain in Gastric and Duodenal Ulcer*, *Arch Int Med* **39** 109 (Jan) 1927.

3 Pick, A. *Wien klin Rundschau* **20** 1, 1906, *Wien klin Wchnschr* **63** 105, 1913.

4 Glaessner, K., and Kreuzfuchs, S. *Munchen med Wchnschr* **60** 582, 1913.

5 Hurst, A. F. *The Sensibility of the Alimentary Canal*, London, 1911, p. 55.

6 Poulton, E. P. *Lancet* **200**:263, 1921.

7 Thomson, A. *Brit M J* **1** 648, 1909.

8 Thomson (footnote 7). Moynihan, B. G. A. *Duodenal Ulcer*, London, 1910, p. 118, *Lancet* **182** 9, 1912.

9 Reynolds, L., and McClure, C. W. *Motor Phenomena Occurring in Normal Stomachs*, *Arch Int Med* **29** 1 (Jan) 1922.

When one examines these hypotheses a little more closely, one finds that Bonninger diagnosed gastric ulcer by putting 100 or 200 cc of tenth normal hydrochloric acid into the empty stomach through a tube. Only patients with ulcer experienced pain, and the healing of the ulcer could be gaged by the lessening of the response to this test. On the other hand, Hurst introduced 0.5 per cent hydrochloric acid into the stomachs of six patients with gastric ulcer, and no sensation whatever was produced. He concluded that "contact with free hydrochloric acid is not the direct cause of the pain in gastric and duodenal ulcer." Ryle¹⁰ reported instances of patients with gastric ulcer who had complete achlorhydria with severe and characteristic pain, and similar instances of duodenal ulcer associated with hypochlorhydria have been described by Moynihan,¹¹ Hardt¹² and others. Recently, however, Palmer reported that the administration of from 200 to 400 cc of 0.5 per cent hydrochloric acid caused pain in several patients with duodenal ulcer and in several with gastric ulcer. He stated that "hydrochloric acid is the normal stimulus to the pain producing mechanism of sensitive peptic ulcers." Pick's suggestion that mechanical irritation of food is the cause of the pain fails to explain the relief obtained when more food is taken or when sodium bicarbonate is ingested. Further, the pain does not occur until most of the meal has passed the site of the ulcer. In 1892, Ewald¹³ suggested that "the surface of the ulcer is distorted and its nerves irritated by the contractions accompanying digestion." In 1913, Glaessner and Kreuzfuchs⁴ found that the pain of duodenal ulcer was due to prolonged "late" pyloric spasm, as evidenced by a persistent clear interval between the gastric and duodenal shadows on roentgen-ray examination. Reynolds and McClure⁹ found that spasm of the pyloric sphincter, as shown by the absence of barium in the cap and duodenum during strong gastric peristalsis, was present in a number of persons with duodenal ulcer during the time of pain. In one patient, however, severe pain was felt while barium was seen to be passing through the sphincter, the next peristaltic wave showed complete pylorospasm, although the pain had ceased. Ginsburg and his associates¹⁴ showed that pain was felt at or after the maximum of hunger contraction, and this was confirmed by Carlson,¹⁵ Hardt¹² and others. This hypothesis failed

10 Ryle, J. A. *Gastric Function in Health and Disease*, New York, Oxford University Press, 1926, p. 118.

11 Moynihan (footnote 8, second reference).

12 Hardt, L. L. J. *Gastric Pain*, J. A. M. A. **70** 837 (March 23) 1918.

13 Ewald, C. A. *Diseases of the Stomach*, New York, 1892, p. 244.

14 Ginsburg, H., Tumpowsky, I., and Hamburger, W. W. *Pain in Gastric Ulcer*, J. A. M. A. **67** 990 (Sept. 30) 1916.

15 Carlson, A. J. *Am. J. Physiol.* **45** 80, 1917.

to explain why patients seldom had pain before breakfast and why in many cases it passed off before the next meal. Further, Homans¹⁶ found that pain may occur independently of muscular activity of the stomach, as judged by changes in the pressure of a balloon in the stomach. Also, Ortmyer¹⁷ showed that no change occurred in the character of the gastric contractions during the relief of pain by alkalis.

That spasm of a part of the stomach may be the cause of pain in some persons with duodenal ulcer is suggested by the observations of Reynolds and McClure,⁹ who describe one case in which duodenal ulcer was associated with an hour-glass contraction of the stomach.

In some of the papers referred to here there is a certain amount of confusion as to the site of the ulcers discussed, since the lesion is termed a "peptic" ulcer, and the exact situation is not stated. It is not certain that the conclusions drawn from a study of gastric ulcers can be applied to those of the duodenum, or vice versa.

A careful study of the work of all the authors consulted shows that the views of the majority may be summarized in two hypotheses namely, that the pain is caused by (a) "acid" or (b) muscle tension. Some authors have combined these by suggesting that acid causes hypertonus and pylorospasm, and have said that in patients with true achylia pylorospasm never occurs.

In support of the acid hypothesis is the fact that the gastric acidity is high in many patients with duodenal ulcer, and also that relief by the administrations of alkalis is an almost universal experience, at least at some period in each patient's history. The statements of Bonninger, Palmer and others that pain follows the administration of from 100 to 200 cc of from 0.36 to 0.5 per cent hydrochloric acid on an empty stomach are strongly in its favor. Further, Sippy and Palmer found constant relief by emptying the stomach in such cases, and in these the gastric contents were markedly acid.

Against the acid hypothesis are the few instances on record of patients with duodenal ulcer in whose gastric contents free acid was not found. In the literature there are also reports of many cases of patients with hypochlorhydria. Hurst, Ginsburg and others failed to produce pain by administering from 0.5 to 1 per cent hydrochloric acid, although Ginsburg found that in one patient the administration of 5 per cent hydrochloric acid was followed by intense pain and vomiting. Reynolds and McClure poured 0.36 per cent hydrochloric acid through a tube directly on a duodenal ulcer producing pylorospasm, cessation

16 Homans, J. *Am J M Sc* **157** 74 1919

17 Ortmyer, M. *Gastric Motor Activity in Patients with Peptic Ulcer*
Arch Int Med **35**.423 (April) 1925

of gastric peristalsis, and duodenal antiperistalsis, but no pain. Hardt even found temporary relief from the administration of 0.3 per cent hydrochloric acid. In Palmer's cases, the pain did not appear for several minutes (from six to twenty-eight) after the introduction of the acid.

The first evidence in favor of the muscle tension hypothesis is the tracings of intragastric pressure of Carlson, Ginsburg and Hardt, showing that pain most frequently appears at or just after a contraction of the musculature of the fundus. In the opinion of Rogers and Hardt,¹⁸ such contractions are violent peristaltic waves. Glaessner and Kreuzfuchs and Reynolds and McClure found pylorospasm or certain types of abnormal muscular activity present during pain, the latter showed that these abnormalities were replaced by more nearly normal muscular activities following the administration of alkalis. Poulton passed tubes into the stomach and duodenum of each patient, and ascribed the relief experienced to equalization of the internal pressure. He also introduced air under pressure and increased the pain.

Against the tension hypothesis is Palmer's roentgenographic evidence that peristalsis and pylorospasm appeared and disappeared without relation to pain. Reynolds and McClure observed one patient in whom pain was present with a patent pyloric sphincter, and a moment later pylorospasm set in and the pain vanished. In a patient with chronic duodenal ulcer, Homans found that powerful contraction of the stomach was present without pain and, on the other hand, that the patient experienced pain during a quiescent interval. Ortmyer, using the same technic, was unable to detect any change in the frequency or extent of the contractions of the stomach during the relief of pain by alkalis.

To throw some light on this problem, direct observations were made under the fluorescent screen on the movements of the stomach and duodenum in patients suffering from duodenal ulcer associated with pain at the time of observation. Considerable difficulty was experienced in securing suitable patients for this investigation because many, including, of course, those in the wards of the hospital, had received treatment, such as rest in bed, suitable diet and alkalis, and were now free from pain. By selecting patients attending the outpatient department who had not received treatment, sixteen who were suitable for this investigation were found in a period of two years. Each patient was given a barium meal and was examined fluoroscopically in the standing position as soon as possible after the onset of pain. Immediately after the fluoroscopic examination and while some barium remained in the stomach, a small tube was passed and some of the gastric contents removed and examined chemically.

18 Rogers, F. T., and Hardt, L. L. J. *Am J Physiol* 38:274, 1915.

In all cases the barium had sedimented so that only the shadow of the greater curvature could be made out. An estimate was made of the amount of the meal remaining in the stomach, and it was found that this varied from 5 to 60 per cent. The stomach was now observed for several minutes to see whether peristalsis could be detected in the greater curvature. Ten of the patients were found to exhibit peristaltic waves, which varied considerably in depth and frequency, being classified as slight, good or very good. Barium was not seen to enter the cap in any case.

After the behavior of the stomach was observed for some minutes, pressure was applied on the abdominal wall, and barium was forced through the pyloric canal into the cap. At first considerable difficulty was experienced in filling the cap, later, as the operator became more

Data of Gastric Contents in Sixteen Cases

| Case No | Onset of Pain After Meal (Min) | Time of Observation After Onset (Min) | Percentage of Meal in Stomach | Peristalsis | Free Acid | Total Acid | Effect of Forcing Contents into Duodenum |
|---------|--------------------------------|---------------------------------------|-------------------------------|-------------|-----------|------------|--|
| 1 | 85 | 5 | 20 | | 68 | 108 | Relief |
| 2 | 75 | 5 | 5 | Slight | 42 | 68 | Relief |
| 3 | 105 | 5 | 30 | None | 52 | 90 | Relief |
| 4 | 105 | 15 | 30 | None | 70 | 94 | Relief |
| 5 | 105 | 30 | 5 | Slight | 98 | 108 | Relief |
| 6 | 115 | 15 | 40 | Very good | 68 | 97 | Relief |
| 7 | 40 | 10 | 30 | Slight | 76 | 96 | Relief |
| 8 | 155 | 10 | 20 | Good | 71 | 82 | Relief |
| 9 | 65 | 30 | 40 | Slight | 75 | 93 | Relief |
| 10 | 80 | 30 | 40 | None | 54 | 78 | Relief |
| 11 | 95 | 10 | 25 | Good | 13 | 40 | Relief |
| 12 | 170 | 15 | 60 | Good | | | Relief |
| 13 | 60 | 105 | 20 | Very good | | | Relief |
| 14 | 95 | 35 | 15 | Good | 78 | 93 | No relief |
| 15 | 40 | 45 | 60 | None | | | No relief |
| 16 | 15 | 15 | 50 | None | | | No relief |

expert in this manipulation, it was found that the cap could be filled with ease on the first attempt in nearly every instance. Subsequent observations showed that the difficulty encountered in the first attempts was due to spasm of the pylorus induced by massage.

In thirteen of the sixteen cases, it was found that filling the duodenal cap by manual pressure on the abdomen was followed almost immediately by relief from the pain. In three instances the pain vanished completely on the first filling of the cap and did not recur. In five cases the pain vanished completely but recurred in a few seconds. In five cases the acuteness of the pain was lessened, leaving a sense of soreness. In the remaining three cases the pain was not relieved when the gastric contents were forced into the duodenum. These are discussed later in the paper. In several of the cases the patient volunteered the statement that his pain had been relieved, in the others, the question "How is the pain now?" met with the response "It is gone," or "It is much better."

The accompanying table shows the time of onset of the pain, the time of observation, the principal fluoroscopic manifestations and the free and total acidity of the gastric contents in these sixteen cases. The last three patients in the list differed from the others, and their protocols and the protocol of an additional patient are given in full.

PROTOCOLS OF LAST THREE CASES IN TABLE

CASE 14—The patient had had epigastric pain from one-half to two hours after meals at intervals for twelve years.

9 50 a m A barium meal was given. The duodenal ulcer close to the pyloric sphincter was confirmed by a series of roentgenograms.

11 55 The patient had had pain for the last thirty minutes with headache. Both the pain and the headache were intermittent.

11 58 Fifteen per cent of the barium meal remained in the stomach. The rate of peristalsis was fairly good, but not nearly as strong as it had been at 9 50 to 10. The pain came and went without any change in peristalsis.

12 02 By means of manual pressure on the abdomen, a little barium was squeezed past the pyloric sphincter. Much pressure was required. The cap could not be filled, but a streak of barium was seen to pass into the second portion of the duodenum. No change in sensation occurred.

12 03 to 12 07 The manipulation was repeated twice. The pain kept coming and going, and was not influenced by pressure or squeezing over except at the last manipulation when, discomfort not being present, squeezing over was followed by pain. Frontal headache also came and went, roughly parallel to the occurrence of epigastric pain.

12 20 A duodenal tube was passed.

12 21 to 12 27 Sixty cubic centimeters of opalescent, white gastric contents containing a little mucus was removed. Free acid was 78 and total acid, 93.

CASE 15—At 10 10 a m, a barium meal was given. The presence of a duodenal ulcer was confirmed by a series of roentgenograms.

11 25 Soreness had been noticed in the epigastrium for the last thirty-five minutes while the patient had been lying down.

11 35 Sixty per cent of the meal remained in the stomach. Peristalsis did not occur. Soreness was not present now.

11 38 Still peristalsis and soreness were not present. Barium was pressed into the cap with moderate difficulty. Soreness ensued. The soreness came and went. Sometimes barium could be pressed into the cap and sometimes it could not. (It was concluded at the time that the soreness was not wholly due to spasm.) The obstruction encountered was not proximal to the pyloric sphincter, since the shape of the gastric shadow was normal. When the gastric contents could be pressed into the duodenum during the soreness, this was eased. Vigorous manipulation apparently caused soreness. There was a constant residue in one small spot of the cap (crater?). Only once was a peristaltic wave seen.

11 55 The observation was concluded.

CASE 16—The patient was 45 years of age.

9 45 a m A barium meal was given. The presence of a duodenal ulcer was confirmed by a series of roentgenograms.

10 00 Pain commenced.

10 15 Fifty per cent of the meal remained in the stomach. The stomach was seen to be in the pelvis, the greater curvature being about 4 inches (10 cm).

below the intercostal line Peristalsis did not occur When the stomach was raised by pressure on the abdomen, the pain vanished When the pressure was released the pain returned This was repeated twice with similar results

10 23 The patient put on his abdominal belt, and at once the pain was eased He stated that he did not feel pain when lying down

With reference to the observation of Reynolds and McClure⁹ that spasm of some part of the stomach may be associated with the pain in some patients with duodenal ulcer, the following is the only instance I have seen which suggests this

CASE 17—The patient had had attacks of epigastric pain about two hours after meals for several years The pain was relieved by food

9 45 a m A barium meal was given Fluoroscopic examination showed a constantly deformed cap This was confirmed by a series of roentgenograms

11 50 Epigastric pain commenced

12 05 The stomach was empty, as seen under the fluoroscope The pain came and went

12 10 The patient was given a barium meal of 8 ounces (227 Gm)

12 11 Gastric peristalsis did not occur, but a definite midgastric constriction was noticed Pain was still present

12 13 The constriction disappeared, as did the pain also Peristalsis began, and the cap filled

12 14 The peristaltic movement was strong The cap was filling

12 20 Well marked peristalsis was present The cap filled at the approach of each wave The patient did not feel any pain

COMMENT

The important fact which emerged from this investigation was that in patients with duodenal ulcer suffering from pain at the time of observation, filling of the duodenal cap with gastric contents by manual pressure on the abdomen was followed by relief from the pain in thirteen of sixteen cases

In eleven of these sixteen cases the gastric contents were strongly acid, the free acidity varying from 42 to 98, and the total acidity from 68 to 108 In all but one of the eleven cases just described the introduction of the strongly acid contents of the stomach into the duodenal cap was followed by relief from the pain There would, therefore, appear to be no direct relationship between the acidity of the gastric contents and the occurrence of pain in patients with duodenal ulcer However, the almost universal experience of relief from the pain of duodenal ulcer by the administration of alkalis suggests that acid in some manner may be a factor in the production of pain

The activities of the musculature of the stomach and duodenum in their relationship to pain may be considered from the following stand-points (1) peristalsis (2) abnormal local contractions (for example, spasmodic hour-glass) (3) general tonic contractions, such as the gradual contraction of the stomach as the contents pass out, (4) resis-

tance to distention ("hold-on"), (5) relaxation (active or passive) The last three may be regarded as manifestations of "tone" or "postural activity" (Sherrington)

The overaction of peristalsis, local or general contractions, or resistance to distention might produce pain, whereas depression of these activities might relieve pain Relaxation might abolish pain

In this investigation, except in case 17, in which localized midgastric contraction was present, there was no relationship between peristalsis, abnormal local contraction, general tonic contraction or resistance to distention and pain in regard to the stomach The fact that the pain was not in waves but was constant is further proof that peristalsis was not the cause It is therefore unlikely that the pain in duodenal ulcer is due to overaction of the musculature of the stomach

In regard to the pyloric sphincter, peristaltic activity can hardly have been the factor causing pain, because the pain was constant and did not occur in waves Neither spasmodic contraction, tonic contraction, nor resistance to distension can be implicated, because in several of the patients the gastric contents could be moved through the sphincter with ease while pain was being felt This indicates that the sphincter was relaxed and that in all probability the pain was not due to the overaction of its musculature Support is lent to this view by the observation in case 14 that the pain was not relieved when the gastric contents passed through the pyloric sphincter but did not distend the caput

It was found extremely difficult to make observations on peristalsis in the duodenum as in every instance the contents passed through quickly However, the pain was constant and did not occur in waves, so it is presumed that the pain was not due to duodenal peristalsis

That abnormal local contraction of the caput is not the sole cause of the pain is evidenced by the constant presence of deformity of the caput in many persons with duodenal ulcer when pain is absent This deformity is due in part to the contraction of scar tissue, but also in part to muscular contraction This is obvious from a comparison of the appearance of an ulcerated duodenum in roentgenograms made after a barium meal, with the relaxed condition of the duodenum as seen on the operating table It is possible that such an abnormal local contraction may by sudden or excessive action give rise to pain, because of the fact that it is involved in a general contraction of the caput

The evidence in favor of the existence of a general contraction of the caput in these cases is as follows

The caput was usually empty, and even when it contained barium it was of small caliber, and the barium rushed through in a narrow stream The relief of pain, following the filling of the caput by manual pressure on the abdomen, suggests that relaxation was the cause of the relief

This is corroborated by the observations in case 14, in which the gastric contents passed through the caput, but did not fill it, and the pain remained.

Therefore, the hypothesis arises that the relief of pain is due to relaxation of the musculature of the caput, and conversely, that the pain is due to overaction of the duodenal caput with or without abnormal local contraction or implication of the pyloric sphincter.

There remains the explanation of the absence of relief in the last three cases in the table. Case 14 is explicable on the ground that the caput was not filled by the manipulation. In cases 15 and 16 the pain was postural, and in all probability was due to traction on inflamed peritoneal attachments.

CONCLUSIONS

- 1 The presence or absence of gastric peristalsis does not bear any relation to the occurrence of pain in duodenal ulcer.

- 2 Pain in duodenal ulcer is nearly always relieved by squeezing gastric contents into the duodenal caput.

- 3 Pain in duodenal ulcer is not directly due to the acidity of the gastric contents.

- 4 The relief from pain in duodenal ulcer is due to relaxation of the musculature of the duodenal caput. Pain in duodenal ulcer is due to sustained contraction of the duodenal caput.

RENAL FUNCTION TESTS WITH SODIUM THIOSULPHATE AND SODIUM IODIDE

AN EXPERIMENTAL COMPARISON WITH THE PHENOL-SULPHONPHTHALEIN TEST *

ADOLPH BOLLIGER, PH D

DETROIT

As reported elsewhere,¹ chronic interstitial nephritis is readily produced in dogs by direct roentgen-ray irradiation of the kidneys. The functional aspect of this experimental disease, as far as the usual tests are concerned, has also been recorded,² and reference has been made to a combined renal function test consisting of the injection of sodium thiosulphate, sodium iodide and phenolsulphonphthalein. The present investigation deals with the excretion of these three substances throughout a course of experimental disease of the kidneys. Subsequently, this combined test was also applied to a large group of normal animals. Observations on normal animals led to an investigation concerning the behavior of normal pregnant animals toward the combined test. The latter are also reported in this paper.

Nyiri³ called attention to the usefulness of sodium thiosulphate as an agent for tests of renal function. He also proposed a combination of the sodium thiosulphate tests with the two hour sodium iodide test by injecting the two substances together.⁴ In the work reported here, Nyiri's combination, previously used only in clinical diagnosis, was adopted and a third test was added to this combination, the phenolsulphonphthalein test, as described by Rowntree and Geraghty.⁵

METHODS

A solution was made up containing 1 Gm of sodium iodide, U S P, 1 Gm of sodium thiosulphate, U S P, and 6 mg of phenolsulphonphthalein in 10 cc of water. The animal was catheterized, and 10 cc

* From the laboratories of the Henry Ford Hospital

1 Hartman, F W, Bolliger, A, and Doub, H P. Experimental Nephritis Produced by Irradiation, *Am J M Sc* **172** 487 (Oct) 1926

2 Hartman, F W, Bolliger, A, and Doub, H P. Functional Studies Throughout the Course of Roentgen-Ray Nephritis, *J A M A* **88** 139 (Jan 15) 1927

3 Nyiri, W. Die Thiosulfatprobe, *Wien klin Wchnschr* **35** 682, 1922

4 Nyiri, W. Kurzfristige, einzeitige Nierenfunktionspruefung, *Wien Arch f inn Med* **9** 511, 1924

5 Rowntree, E G, and Geraghty, J T. The Functional Activity of the Kidney, *J Pharm & Exper Therap* **50** 580, 1910

of the solution was injected intravenously. Two hours after injection the animal was catheterized again, and the bladder was irrigated in order to obtain the complete output. The two hour sample of urine, including the wash water, was then made up to a known volume and examined for its sodium thiosulphate content, its iodine content and its phenolsulphonphthalein content.

Nyiri³ described a technic for the determination of sodium thiosulphate and sodium iodide. His technic was modified in these experiments somewhat in order to shorten his rather lengthy procedure for the determination of the iodine output and in order to improve the determination of sodium thiosulphate. To remove iodine absorbing substances, Nyiri purified the urine with pure charcoal for from two to three minutes. Unfortunately, charcoal rapidly absorbs sodium thiosulphate. To remove this source of error, Lloyd's reagent was substituted. This does not absorb any appreciable amount of sodium thiosulphate even if it is left for many hours. Sodium thiosulphate was then determined by titration with hundredth-normal iodine solution.

The same urine fraction which has been purified with Lloyd's reagent can also be used for the determination of iodine. This saves the removal of iodine absorbing substances with 2 per cent ferricchloride as proposed by Singer⁶ and adopted by Nyiri, and iodine is determined directly, according to the method of Singer, by liberation with nitrous acid and extraction of carbon bisulphide. In the work reported here, for convenience, carbon bisulphide was replaced by carbon tetrachloride and the iodine output determined colorimetrically with a set of standards in a comparator. A titration method that consumed considerable time was proposed by Nyiri for determining the liberated iodine in carbon bisulphide.

The tests were carried out in the following manner:

Two hours after the initial injection into a dog, 80 cc of urine, for example, was obtained by catheterization. The bladder was irrigated, the wash water was included and the entire volume was made up to 200 cc. The specimen was at the same time acidified with dilute sulphuric acid. The phenolsulphonphthalein serves as an indicator for the requisite acidity, turning yellow as soon as the specimen is acid. Twenty cubic centimeters (one tenth) of the entire volume of urine was made up to 100 cc., and alkalinized, and the phenolsulphonphthalein was read against a set of standards. The remainder of the urine was shaken with about 5 Gm of Lloyd's reagent and filtered. Twenty cubic centimeters of the filtrate was used for determination of the sodium thiosulphate output. This fraction was titrated with hundredth-normal iodine solution, starch being used as an indicator. The end-point is sharply indicated by a changing of the yellow solution to a bluish green, which has to remain thus for at least two seconds. The other 20 cc of the filtrate was used for the determination of the iodine. This fraction is trans-

6 Singer, H. *Methodisches zur quantitativen Bestimmung des Jodkali*, Ztschr f klin Med 48 157, 1903

ferred to an extraction funnel. About 7 cc of carbon tetrachloride was added with a few drops of a solution of sodium nitrite in concentrated sulphuric acid. The liberated iodine was extracted with the carbon tetrachloride, care being taken not to shake too hard in order to avoid emulsion. The urine was again extracted with a smaller portion of carbon tetrachloride until iodine was no longer demonstrable. The lavender colored carbon tetrachloride solution was made up to a known amount and compared with standards made up by dissolving known amounts of iodine with carbon tetrachloride.

It is well known that hundredth-normal iodine solution is not stable over a long period. This solution may be standardized quickly against the thiosulphate-iodide-phenolsulphonphthalein solution used for this functional test. The number of cubic centimeters of hundredth-normal iodine solution required by 20 cc of 0.5 per cent solution of the original combined substances (10 cc test solution diluted to 200 cc) will give that figure to be used in calculating the percentage of thiosulphate present in 20 cc of urine, the volume of which has previously been made up to 200 cc.

As has been pointed out previously, Lloyd's reagent does not absorb any sodium iodide or sodium thiosulphate. Further, this reagent does not absorb any of the phenolsulphonphthalein dye. The phenolsulphonphthalein content could also be determined to advantage on a urinary filtrate treated previously with Lloyd's reagent, because Lloyd's reagent removes to a large extent other coloring matters and colloidal suspensions which do interfere with the estimation of the phenolsulphonphthalein output.

The combined injection of sodium thiosulphate, sodium iodide and phenolsulphonphthalein will be spoken of as the combined test in the following experiments. It was applied to (A) normal dogs and dogs with extrarenal lesions, (B) normal dogs during gestation, and (C) dogs with experimental nephritis produced by deep roentgen rays.

EXPERIMENTS

A Normal Dogs and Dogs with Extrarenal Lesions—Table 1 includes a series of fifteen normal female animals to which the combined test has been applied. The thiosulphate output in two hours varies from 50 to 66 per cent after the injection of 1 Gm of sodium thiosulphate, U S P. I consider this as the normal range of thiosulphate output for dogs. This table further includes a depancreatized dog, a dog with distemper and a morphinized animal. The thiosulphate output of the animals with extrarenal lesions lies also between the normal range, i. e., from 50 to 66 per cent. The iodine output after the administration of 1 Gm of sodium iodide varies from 0 to 95 mg in two hours. The majority of the observations showed an output of between 40 and 80 mg in two hours.

Table 2 represents a dog which had, during the period of observation, extensive roentgen-ray treatment over the chest. The animal developed a lesion of the heart as proved by electrocardiograms and at autopsy. The electrocardiograms showed tachycardia and auricular flutter, and at autopsy hemorrhages and hyaline degeneration were found throughout the right auricle. Before and during the experiment, several combined tests were performed over a period of three months. The phenolsul-

TABLE 1—Results of Tests in Normal Dogs and Dogs with Extrarenal Lesions

| No | Phenolsulphonphthalein (Per Cent) | Iodine Excretion (Mg) | Sodium Thiosulphate (Per Cent) | Urea | |
|----|-----------------------------------|-----------------------|--------------------------------|------|---|
| 1 | 70 | 40 | 56.4 | 15.4 | |
| 1 | 78 | 203 | 55.6 | 11.4 | Two days after irradiation over left kidney |
| 2 | 65 | 45 | 53.5 | | |
| 2 | 70 | 78.7 | 51.0 | | |
| 3 | 60 | 50 | 58.5 | | Depancreatized blood sugar, 430 Gm |
| 4 | 70 | 70 | 64 | | |
| 4 | 70 | 50 | 63.0 | | |
| 5 | 70 | 50 | 58 | | |
| 6 | 70 | 45 | 59.5 | | |
| 7 | 65 | 56 | 61.7 | | |
| 8 | 65 | 0 | 62 | | |
| 8 | 65 | 80 | 50 | | Distemper, died three days later |
| 9 | 65 | 61 | 47.3 | | |
| 10 | 70 | 61 | 63.4 | | |
| 10 | 70 | 95 | 65.9 | | After morphine, 1 grain (0.065 Gm) |
| 11 | 70 | 0 | 53.5 | | |
| 12 | 70 | 5 | 55.3 | | |
| 13 | 60 | 45 | 51.2 | | |
| 14 | 70 | 55 | 55 | | |
| 15 | 65 | 60 | 56 | | |
| 16 | 75 | 25 | 54 | | |
| 17 | 70 | 80 | 62 | | |

TABLE 2—Results of Tests in Dog with Cardiac Lesion

| Date | Phenolsulphonphthalein (Per Cent) | Sodium Thiosulphate (Per Cent) | Iodine Excretion (Mg) | Urea |
|---------|-----------------------------------|--------------------------------|-----------------------|------|
| 5/20/26 | 70 | 63 | 61 | 15.4 |
| 5/27 | 70 | 66 | 95 | |
| 7/7 | 70 | 71 | 28 | 14.5 |
| 7/13 | 70 | 67 | 600 | 18.2 |
| 8/24 | 65 | 72 | 544 | 14.1 |

phonphthalein output did not change. The sodium thiosulphate output became increased in the last month of the experiment. The excretion of iodine was found to be as high as 600 mg during the period when the animal showed marked tachycardia.

Table 3 represents an animal with a persistent albuminuria which was followed over a period of three months. The animal appeared to be healthy in every respect, and an explanation for the albuminuria could not be found. The phenolsulphonphthalein output remained between normal limits throughout the whole experiment. The sodium thiosul-

phate output did not reveal any functional disturbances, and the iodine excretion varied from 11 to 230 mg in two hours

B Normal Dogs During Gestation—The following observations were made on three animals which were pregnant when obtained for the laboratory. They were under observation for a number of months and bore an apparently full term litter. Two of the animals were considered entirely normal, but the third animal had had one kidney removed before observations were started.

Chart 1 illustrates a large normal dog which showed, fifty-one days before delivery, a phenolsulphonphthalein output of 70 per cent, a thiosulphate excretion of 60 per cent and an iodine excretion of 57 mg. Up to delivery six more combined tests were done at varying intervals. The phenolsulphonphthalein test did not show any consistent fluctuations but remained within normal limits throughout the experiment. Forty-three days before delivery the sodium thiosulphate output was markedly

TABLE 3—*Results of Test in Dog with Persistent Albuminuria*

| Date | Phenolsulphophthalein (Per Cent) | Sodium Thiosulphate (Per Cent) | Iodine Excretion (Mg) | Urea |
|---------|-------------------------------------|--------------------------------------|-----------------------------|------|
| 3/22/26 | 65 | 52 | 90 | 15.4 |
| 3/27 | 70 | 55 | 55 | 12.1 |
| 3/31 | 70 | 57 | 109 | |
| 5/5 | 70 | 52 | 128 | 12.0 |
| 5/7 | 70 | 50 | 11 | 12.1 |
| 5/10 | 70 | 56 | 36 | 11.0 |
| 5/22 | 75 | 60 | 90 | 17.7 |
| 6/8 | 72 | 63 | 44 | |
| 6/18 | 70 | 52 | 230 | 17.9 |
| 6/30 | 65 | 60 | 27 | 12.6 |

diminished, i. e., 46 per cent, and the iodine output was somewhat diminished also. Thirty-five days before delivery the sodium thiosulphate output was only 40 per cent, and there was no iodine output during the two hours of the test. Twenty-one days before delivery the sodium thiosulphate output was at its lowest level, i. e., 33 per cent, and the iodine output was still 0. Eight days before delivery the thiosulphate output started to increase again (37 per cent). The test for iodine became positive, i. e., 28 mg was present. Eighteen hours before delivery the thiosulphate output was nearly normal, i. e., 47 per cent, and the iodine excretion was 156 mg. The animal was delivered of nine living pups and had a normal postpartum course. One month after delivery, the sodium thiosulphate output was found within normal range and the iodine output was 92 mg. Two weeks later, the output of thiosulphate and of phenolsulphonphthalein was still found to be within normal range.

Chart 2 represents a similar animal. About one month before delivery, a marked depression in the sodium thiosulphate output was found, with a recovery to normal after delivery. The iodine output was some-

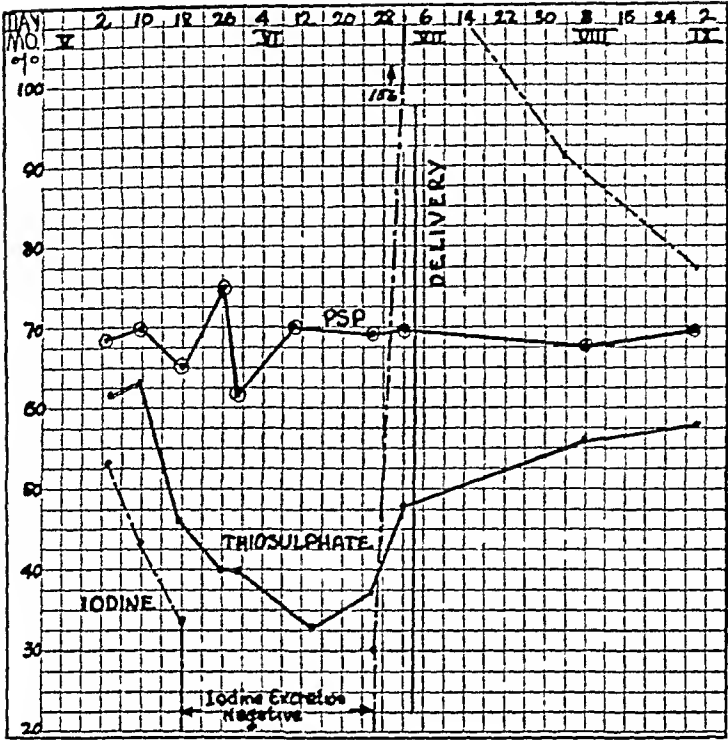


Chart 1—Results of test in a large normal pregnant dog In this chart and in charts 2, 3 and 4, PSP indicates phenolsulphonphthalein

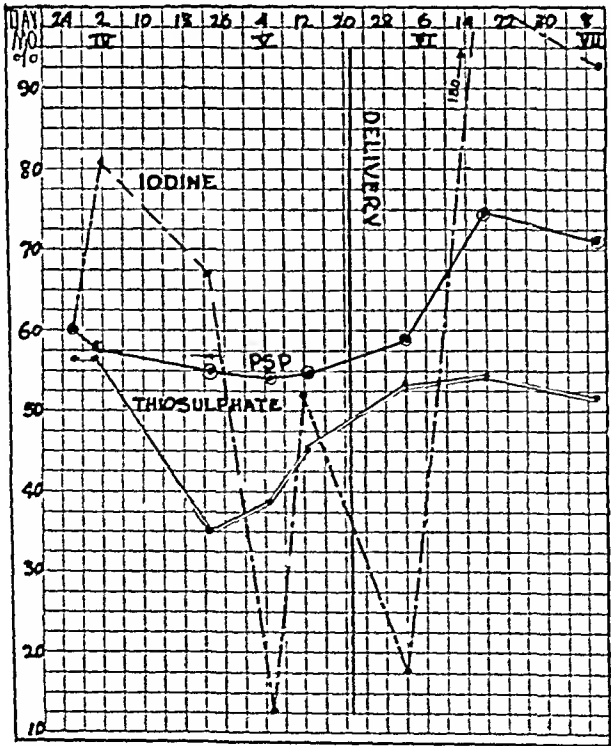


Chart 2—Results of test in an animal similar to the one shown in chart 1

what irregular, reaching the low level of 12 mg about two weeks before delivery, about one week before delivery, the iodine output was 54 mg, and dropped to 20 mg about twelve days after delivery. In this case, also, a slight depression in the phenolsulphonphthalein output could be made out (53 per cent at its lowest point), coincident with depression in the thiosulphate output.

Chart 3 represents the dog in which the left kidney was removed a short time before impregnation. The thiosulphate output was found to be depressed when the observations were started, about one and one-half months after operation and forty-six days before delivery. Thirty-three days before delivery the sodium thiosulphate output was only 30 per cent, and this dropped down to 23 per cent in the next few days. A week later, there was a slow, steady improvement in the puerperium, and the output of thiosulphate had increased to 48 per cent nineteen days after delivery. A depression in the iodine output was found about five weeks before delivery. The phenolsulphonphthalein output was also somewhat depressed, as in the previous experiment.

C Dogs with Experimental Nephritis Produced by Deep Roentgen Ray—The pathologic changes in nephritis as produced by deep roentgen rays have already been described. The condition has been subdivided, for the purpose of study, into the acute, subacute and chronic stage. The combined test was applied to all these stages, as can be seen in chart 4. This chart demonstrates a moderately rapid progressive nephritis which was produced by irradiation of both kidneys through the abdominal wall. The course of the disease is well depicted by the phenolsulphonphthalein output. Nearly one month after irradiation the phenolsulphonphthalein output remained within normal levels, and from previous experience this might be considered the acute and the subacute stages of the disease. During the next fourteen days a marked depression of the phenolsulphonphthalein output was noticed, reaching 35 per cent about one and one-half months after irradiation. For the next two months the fluctuations were moderate, and this might be considered as the chronic stage. During the last month of the animal's life, a further marked depression was noticed, which could be considered as the late chronic stage. The thiosulphate output was practically parallel with the output of phenolsulphonphthalein throughout the disease. A subnormal thiosulphate output was found in the subacute stage, while the phenolsulphonphthalein output was still normal. The parallelism between the thiosulphate output and the phenolsulphonphthalein output was found throughout until the late chronic stage, when the phenolsulphonphthalein output became more depressed than the thiosulphate output. The iodine output showed large fluctuations and there was an agreement only between the phenolsulphonphthalein and the iodine

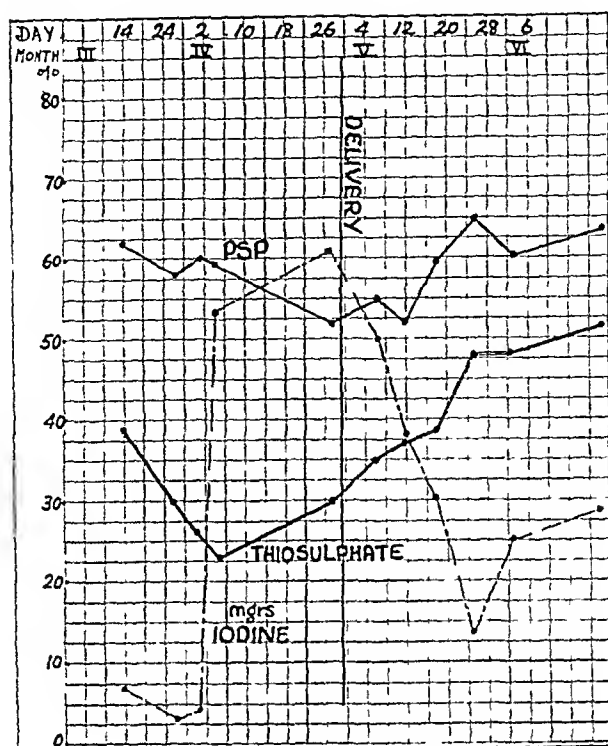


Chart 3—Results of test in a dog in which the left kidney was removed a short time before impregnation

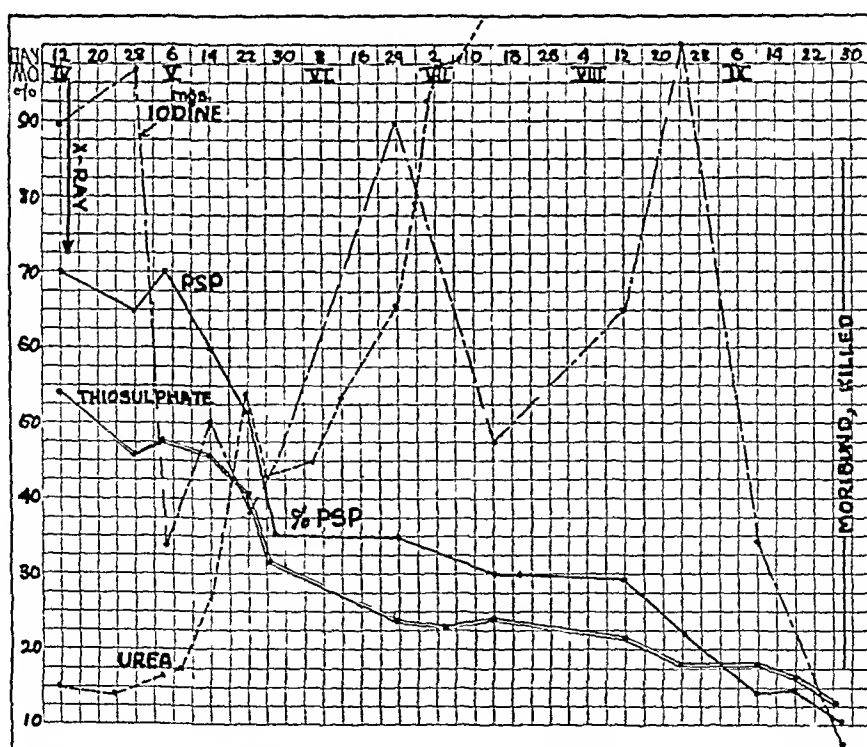


Chart 4—Results of combined test as applied in acute, subacute and chronic stage

output in the terminal stage, both being low. The iodine excretion was found to be high soon after irradiation.

Chart 5 represents an animal with a rapidly progressing nephritis terminating in uremia. The left kidney was irradiated directly through a surgical incision. A month later the right kidney was removed and a

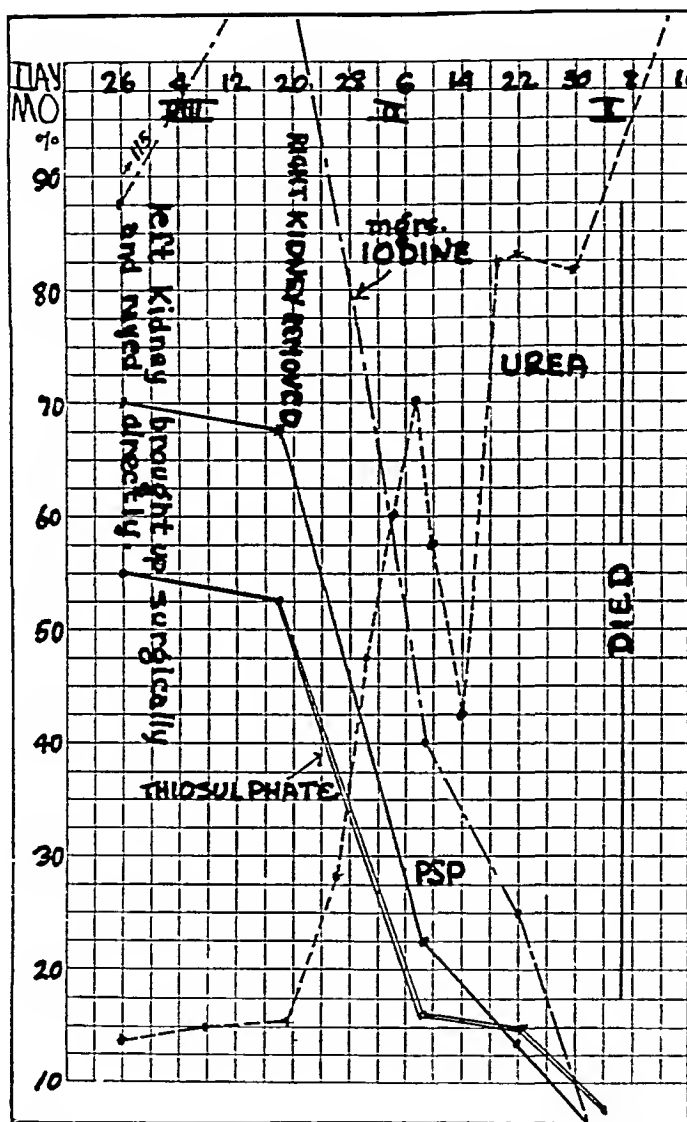


Chart 5—Results of test in an animal with a rapidly progressing nephritis terminating in uremia

sudden fall in the phenolsulphonphthalein and thiosulphate outputs was noticed together with a rapid increase in the urea nitrogen content of the blood. As confirmed in a number of similar experiments, the directly irradiated kidney becomes fibrosed rapidly and a lethal insufficiency is produced as soon as the nonirradiated kidney is removed. In spite of the short irradiation, this animal died a month after removal of the non-

irradiated kidney The same parallelism between thiosulphate and phenolsulphonphthalein excretion was found in rapidly progressing nephritis In the late stage, ten days before death, the thiosulphate output became more depressed than the phenolsulphonphthalein output Two days before death, the phenolsulphonphthalein output was 2 per cent and the thiosulphate output was 6 per cent In this type of experiment, the iodine output also is roughly parallel with the phenolsulphonphthalein and thiosulphate outputs The iodine output increased after irradiation and after removal of the nonirradiated kidney The iodine output dropped to 40 mg twenty-four days before death and to 25 mg ten days before death and only a trace was present two days before death

TABLE 4—*Results of Test in Dog with Slowly Progressing Interstitial Nephritis*

| Date | Phenolsul- phonphthalein (Per Cent) | Sodium Thiosulphate (Per Cent) | Iodine Excretion (Mg) | Urea | |
|---------|---|--------------------------------------|-----------------------------|------|---------------------------|
| 1/29/26 | 65 | | | 14 | |
| 1/29 | Irradiation over both kidneys | | | | |
| 3/23 | 45 | 39 | 12 | 13.5 | Distemper and mange |
| 3/27 | 50 | 39 | 10 | | |
| 3/31 | 45 | 38 | 24 | 12.6 | |
| 4/3 | 55 | 40 | 24 | 18.7 | |
| 4/28 | 50 | 43 | 43 | | |
| 5/5 | 50 | 40 | 5 | 14 | |
| 5/13 | 52 | 43 | 20 | | |
| 5/21 | 70 | 43 | 28 | 19.6 | |
| 6/2 | 50 | 36 | 70 | 28.5 | |
| 6/7 | 45 | 26 | 33 | 31.8 | |
| 6/24 | 45 | 25 | 80 | 35 | Carbon dioxide — 53 |
| 7/14 | 55 | 34 | 64 | 35 | |
| 8/9 | 55 | 34 | 30 | 42 | |
| 8/22 | 40 | 28 | | 41 | |
| 9/30 | 55 | 34 | | 45 | Carbon dioxide — 51 |

Table 4 represents a dog with a slowly progressing interstitial nephritis Roentgen-ray irradiation was given once over both kidneys through the abdominal wall About two months after irradiation the experimental disease became complicated by distemper and mange, but the animal recovered from these complicating factors, and the disease took the slow path of chronic interstitial nephritis as frequently seen in human beings

The phenolsulphonphthalein output was found to be depressed as soon as observations were started, about a month after irradiation With a few exceptions, the output of dye averaged about 50 per cent during the next six months of observation The sodium thiosulphate output was markedly depressed during the period of distemper but increased somewhat and averaged about 30 per cent in the last three months of the experiment The excretion of iodine was inconsistent as was seen in other experiments of this type, but the amounts of urea nitrogen began to increase slowly during the last four months of observation

COMMENT

Nyiri described the two hour sodium iodide test as a simple, practical test of renal function. This statement is based on fifty-four observations of normal patients without renal disease and on twenty-six patients with renal insufficiency. The observations on dogs in these experiments do not substantiate those of Nyiri. Animals without renal involvement showed great variations in the iodine output, and animals with proved disease of the kidneys frequently did not show any relation between the state of the disease and the quantitative iodine output two hours after intravenous administration. There was an agreement only between the iodine excretion and an existing renal insufficiency in the late stages, but it was found that the test did not have any diagnostic value in experimental chronic nephritis of dogs.

The hypothesis of Nyiri and earlier workers that the kidneys are the main factor in the urinary excretion of sodium iodide was shown to be correct only in the late stages. The excretion of iodides was frequently not taken up for two or more hours after the intravenous administration in apparently normal animals. After the excretion had started, whether it was delayed or occurred immediately after administration, frequently a relation between the rate of excretion and the concentration of sodium iodide in the blood and tissues could not be demonstrated. Finally, the entire time required to eliminate completely the injected sodium iodide did not give any information regarding activities of the kidney. Some other activities of the body, as shown, for example, in pregnancy, seem to have a far greater influence on the excretion of sodium iodide during the first two hours and also in later periods after the injection of sodium iodide. It is thought that this simple and accurate procedure may find its application in another field.

Like sodium iodide, sodium thiosulphate is found in the normal animal in small amounts, however, it does not follow the excretory properties of sodium iodide but shows a striking similarity in its excretion curve to phenolsulphonphthalein in all experiments with experimental chronic nephritis. Whether the depression of sodium thiosulphate as seen during pregnancy is also accompanied by a similar depression of the phenolsulphonphthalein output is not clear from these experiments, but this discrepancy may be explained by the fact that small functional changes in the kidneys are usually more accurately registered by the thiosulphate test than by the phenolsulphonphthalein test. This is mainly due to the following two facts: first, the thiosulphate output is determined by a more accurate procedure than the phenolsulphonphthalein output, i.e., titration of standardized iodine solution, second, thiosulphate injected intravenously in unchanged form is practically completely excreted in two hours by the normal kidney and by the kidney in which

excretion is insufficient Thiosulphate that is injected but not excreted is oxidized to sulphate and is excreted as such

Of course, it may just as well be assumed that the depression of the thiosulphate excretion during pregnancy, as described in three animals and as observed in the meantime on two other dogs, is not at all or only partly connected with the activity of the kidney The depressed excretion may be considered as the expression of the altered metabolism of pregnancy and may have a useful application in the diagnosis of pregnancy

On the other hand, it should also be pointed out that the sodium thiosulphate furnishes results averaging from 2 to 3 per cent above the theoretical value This is due to the fact that the iodine combining substances of the urine are not entirely removed either by treatment with Lloyd's reagent or charcoal There is a variation in the remaining amount of iodine combining substances in the different urines, in general, following the specific gravity of the urine An attempt was made to overcome this difficulty by diluting all urines up to a standard amount and titrating at about the same p_H The small possibility of error seems to be well corrected by these procedures, as can be seen by the consistency of results in the protocols On the other hand, the fact that the results obtained are somewhat too high may explain the higher output of sodium thiosulphate as compared to phenolsulphonphthalein in renal insufficiency that has progressed far A thiosulphate output of 0 is rarely encountered

Nyiri proposed a correction for this inaccuracy by determining the iodine combining power of urine (treated accordingly) previous to the experiment I consider this correction only a complication of an experimental procedure, since the urine obtained after administration of thiosulphate and water (diuresis) will have other properties than urine obtained previous to the test

Only about two thirds of the dosage as originally proposed by Nyiri was injected He used 1 Gm of anhydrous sodium thiosulphate, and I injected 1 Gm of sodium thiosulphate U S P containing 6 molecules of water of crystallization or only 0.68 Gm of anhydrous sodium thiosulphate This dosage could be reduced further without impairing the accuracy of the results, but it might be pointed out that in these experiments harmful effects, even in animals in which the renal insufficiency had progressed far, were never observed The diuresis produced immediately after the administration of sodium thiosulphate is of decided value in experimental work, since water does not have to be administered by stomach tube in order that a sufficiently large quantity of urine may be obtained Diuresis itself does not vitiate the results of the test, since the observations in animals with spontaneous diuresis in the earlier stages of chronic interstitial nephritis show consistent results

After the phenolsulphonphthalein test was added to the combined renal function test of sodium iodide and sodium thiosulphate, the sodium iodide test was found to be of minor value in tests of renal function. Now, I am using a combination of the sodium thiosulphate test and the phenolsulphonphthalein test. This combination was found satisfactory in experimental work on animals.

I think that this combination will also be of help in clinical work in spite of the fact that the two hour sodium thiosulphate excretion is remarkably smaller in normal human beings than in normal dogs (from 30 to 40 per cent). Nyiri and Eskelund reported gratifying results in clinical cases.⁷

SUMMARY

1 A combination of three renal function tests, consisting of the sodium thiosulphate test, the sodium iodide test and the phenolsulphonphthalein test, was studied experimentally. It was applied to normal, pregnant and nephritic dogs and to dogs with extrarenal lesions.

2 The sodium thiosulphate test is found to be a specific quantitative test for experimental renal insufficiency, it gives essentially the same information as the phenolsulphonphthalein test. It is also somewhat more accurate and may better detect slight lesions in the kidneys.

3 Pregnant dogs show a depression in sodium thiosulphate output.

4 The two hour sodium iodide test is of little value in tests of renal function.

⁷ Eskelund, V. Kidney Function Test with Sodiumthiosulphate, *Hospital-stid* 68 217, 1925.

EFFECT ON BASAL METABOLISM OF LIGATING LOWER EXTREMITIES *

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AND

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There is a law of surface energy which says that the production of heat in different animals is essentially constant per unit of body surface. The idea that there is an intimate relationship between body surface and production of heat was first observed by French writers¹ as early as 1839. The body surface law was definitely formulated in 1847 by Bergmann². In 1883, Rubner³ and Richet⁴ published almost simultaneously the first modern experimental data on the subject, and, because Rubner's work was considered the more important, the body surface law has since been known as Rubner's law.

In the beginning, most physiologists held the conception of a causal relationship between heat production and body surface. From time to time, however, even the most ardent advocates of the body surface law have admitted discrepancies, and its universal applicability has been challenged. Factors such as age, prematurity, prepubescence, sex, athletic training, level of nutrition and pathologic states cause differences in production of heat which cannot be explained on the basis of differences in body surface. The conception, therefore, of a causal relationship between basal metabolism and body surface has come to be abandoned by most physiologists, and instead, the surface area has come to be considered merely the most exact available biometric measurement of basal metabolism.

Researches point to a simple mathematical relationship between production of heat and many bodily functions, a relationship which may be expressed by the simple formula $P \propto \sqrt[3]{W}$, or the square of the cube root of the body weight, which formula seems to represent a definite general morphologic law of growth. In 1888, von Hoesslin⁵ recognized that the

* From the Pediatric Service of Mount Sinai Hospital, chief of staff, Dr. Bela Schick.

1 Sarrus and Rameaux. Bull. Acad. roy. de méd. Paris **3**, 1094, 1839.
Regnault and Reiset. Ann. de chimie et de physique, ser. 3, **26**, 299, 1849.

2 Bergmann, Carl. Ueber die Verhältnisse der Wärmeökonomie der Thiere zu ihrer Grösse, Göttingen, Vandenhoeck und Ruprecht, 1848.

3 Rubner. Ueber den Einfluss der Körpergrösse auf Stoff und Kraftwechsel, Ztschr. f. Biol. **19**, 545, 1883.

4 Richet. Recherches de calorimétrie, Arch. de Physiol., ser. 3, **15**, 237, 1885.

5 Von Hoesslin. Ueber die Ursache der scheinbaren Abhängigkeit des Umsatzes von der Grösse der Körperoberfläche, Arch. f. Anat. u. Physiol., Physiol. Abteil., 1888.

body surface law was but a single application of this general law of growth. Other workers soon questioned the Rubner law. Voit⁶ believed that the production of heat is proportional to the mass of living cells and their power to decompose materials, and should not be identified with body surface. Dreyer⁷ called attention to the correlation between the cross-section of the trachea and the aorta and the surface area of the body. Moulton⁸ observed that the surface area in cattle is proportional to the total body nitrogen, and therefore to the protoplasmic mass. Peabody and Wentworth⁹ found a close agreement between surface area and vital capacity. Pfaundler¹⁰ noted that the Rubner law failed to apply to atrophic individuals whose skin hung in folds. Pirquet¹¹ looked for a surface other than the outer surface of the body mentioned by Rubner in order to find a simpler measure of the nutritional needs of the body.

Thus it is seen that there are many components of the body nearly proportional to the surface area. It is possible that all body cells show this similar proportionality because they are similarly affected by the metabolism and need of the body for oxygen.

Benedict,¹² who is probably the strongest opponent of the Rubner law, says that basal metabolism is a function of the total mass of active protoplasmic tissue. He believes that "if heat production is proportional to the square of the cube root of the body weight, it is not due to the fact that the surface area determines thermolysis, but that the mass of active protoplasmic tissue with probably the same mathematical relationship to the body weight determines thermogenesis."

Helmreich¹³ is in accord with Carl Voit and Benedict in believing that metabolism is determined, not by body surface, but by the active protoplasmic mass. In order to prove this theory, he believes cases

6 Voit, Carl. *Munchen med Wchnschr* **49** 233, 1902.

7 Dreyer, Ray, and Walker. *Proc Roy Soc Med* **86** 39, 1912-1913.

8 Moulton. *J Biol Chem* **24** 299, 1916.

9 Peabody, Francis, and Wentworth, John A. *Clinical Studies of the Respiration*, *Arch Int Med* **20** 443 (Sept) 1917.

10 Pfaundler. *Korpermasstudien V*. *Ztschr f Kinderh* **14**, 1916.

11 Pirquet. *Sitzhöhe und Körpergewicht*, *Ztschr f Kinderh* **14** 211, 1916, *System der Ernährung*, Berlin, 1917. Schick, B. *Das Pirquetsche System der Ernährung und seine Gegner*, *Ztschr f Kinderh* **28** 62, 1921.

12 Harris, J. A., and Benedict, F. G. *Biometric Study of Basal Metabolism in Man*, publ 279, Carnegie Inst, Washington, 1919. Benedict, F. G. *J Biol Chem* **20** 263, 1915. Benedict and Talbot. *Metabolism and Growth from Birth to Puberty*, publ 302, Carnegie Inst, Washington, 1921, publ 201, 1914, publ 233, 1915.

13 Helmreich, E. *Die Unabhängigkeit des basalen Kraftwechsels von der Körperoberfläche*, *Ztschr f d Ges exper Med* **53** 578, 1926, *Der Kraftwechsel des Kindes*, Vienna, Julius Springer, 1927.

should be studied in which a disunion between mass and surface has been affected. In 1916, Pfaundler¹⁰ first suggested the possibility of effecting such a disjunction, but his work involved operative procedure on small animals with long ears and long tails. In 1917, Aub and DuBois¹⁴ studied the metabolism of two legless men to determine whether the Rubner law applied. But they did not have figures before amputation for comparison with those obtained after amputation. Furthermore, amputation creates a pathologic condition.

Helmreich conceived a method of excluding large parts of the body mass from the general circulation without producing a pathologic state, which would at the same time allow a comparison of metabolism before and after such exclusion. His method was as follows:

He ligated an extremity so tightly as to occlude the venous and arterial circulation. In this way, the extremity was withdrawn for the time as an active protoplasmic mass, just as though it had been amputated. The outer surface, however, was not affected, and the nerve connection between the ligated area and the rest of the surface remained unbroken, as was demonstrated in the experiment. If metabolism bears a causal relationship to body surface, it must remain unchanged during the ligation period. If metabolism is a function of active protoplasmic tissue, it must decrease when part of the protoplasmic mass is inactivated through ligation. Helmreich found in all cases a decrease in metabolism which was roughly proportional to the weight of the part ligated, as measured by its volume of water displacement, and not proportional to the surface.

In order to prove that the surface remained intact, Helmreich applied thermal stimuli in the form of ice or ice water to the ligated extremity as well as to the extremity without ligation, and found an increase in metabolism in both cases in response to the external cold.

Helmreich concluded that basal metabolism is a function of the active protoplasmic mass, and not of the body surface. The surface, in its capacity of receptor organ for tactile, pain and thermal stimuli, influences the height of metabolism, but should not be identified with metabolism.

We duplicated Helmreich's experiments. One of us (A. T.) attempted the work with several children, but found that the pain and excitement caused by ligation proved so disturbing emotionally that the children could not remain quiet, and therefore the figures obtained were not truly basal. We then decided to try the experiment on each other.

METHOD

We followed Helmreich's method closely, except that whereas he took two minute readings, we took four or five minute readings. The Krogh calorimeter was used. After a fourteen hour fast, and under the usual resting conditions, a

14 Aub, J. C., and DuBois, E. F. Basal Metabolism of Dwarfs and Legless Men, *Arch Int Med* **21** 840 (May) 1917. DuBois, E. F. Basal Metabolism in Health and Disease, ed. 2, Philadelphia, 1927, P. 119. DuBois, D., and E. F. A Formula to Estimate the Approximate Surface Area, *Clinical Calorimetry*, *Arch Int Med* **17** 863 (June) 1916.

determination of the basal metabolism was made. A half inch rubber ligature was then applied to one or both extremities, high up under the symphysis, so tightly as to occlude the dorsalis pedis artery. The ligature was left on for five minutes, and with the ligature still on, another metabolism test was made. The ligature was then withdrawn, and metabolism tests were made at short intervals until the normal basal metabolism was again reached. This procedure was repeated on each of us on six different days. The right extremity was ligated three times, the left one twice, and both extremities once.

On another occasion, with the ligature applied, the extremity was packed in ice from toes to hip, and determinations of metabolism were made as before. This procedure was followed without ligation another day.

Table 1 shows the effect of ligation on our basal metabolism. Table 2 shows Helmreich's results.

TABLE 1—*Effect on Basal Metabolism of Ligating the Lower Extremities (Topper and Mulier)*

| Date | Part Ligated | Kilo-grams of Body Weight | Weight of Leg in Kg * | Pro-portion of Body Weight | Body Surface, Sq M † | Surface of Ligated Part in Sq Cm ‡ | Pro-portion of Body Surface | Basal Metabolism, Total Calories for 24 Hour Period | De-crease During Liga-tion | Per-centage Decrease |
|----------|--------------|---------------------------|-----------------------|----------------------------|----------------------|------------------------------------|-----------------------------|---|----------------------------|----------------------|
| A. T. | | | | | | | | | | |
| May 26 | Right leg | 56.8 | 7.25 | 12.7% | 1.58 | 2,875 | 18.2% | 1,298 | 154 | 11.9 |
| June 6 | Right leg | | | | | | | 1,300 | 150 | 11.6 |
| 9 | Right leg | | | | | | | 1,246 | 135 | 10.8 |
| 14 | Left leg | | | | | | | 1,262 | 153 | 12.5 |
| 23 | Left leg | | | | | | | 1,186 | 150 | 12.6 |
| Oct 26 | Both legs | | 14.5 | 25.4 | | 5,749 | 36.4 | 1,455 | 435 | 27.8 |
| H. M. | | | | | | | | | | |
| April 14 | Right leg | 72.7 | 8 | 11 | 1.75 | 3,037 | 17.4 | 1,400 | 148 | 10.5 |
| 21 | Right leg | | | | | | | 1,380 | 160 | 11.6 |
| May 21 | Right leg | | | | | | | 1,390 | 153 | 11 |
| June 13 | Left leg | | | | | | | 1,344 | 140 | 10.4 |
| 24 | Left leg | | | | | | | 1,388 | 138 | 10 |
| 27 | Both legs | | 16 | 22 | | 6,074 | 34.8 | 1,464 | 294 | 20 |

* Measured by volume of water displaced.

† DuBois height-weight formula (DuBois, D. and DuBois, E. F. A Formula to Estimate the Approximate Surface Area if Height and Weight be Known, Arch. Int. Med. 17: 863 [June] 1916).

‡ DuBois linear formula (DuBois, E. F. Metabolism in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1927).

RESULTS WITH COMMENTS

Table 1 shows a decrease in basal metabolism of from 10 to 12 per cent when one extremity was ligated and a decrease of from 20 and 28 per cent when both lower extremities were ligated. This decrease in basal metabolism was roughly proportional to the mass ligated and not to the surface.

The decrease in metabolism lasted only as long as the mass remained ligated. As soon as the ligature was removed, there was an increase in basal metabolism above the normal level, and only after ten minutes did the metabolism return to normal. Helmreich explains this increase above normal by the oxidation of a mass of blood and lactic acid withheld during ligation. The lactic acid had been formed in the muscles of the ligated extremity as a result of local anemia.

Charts 2 and 3 show how the body surface, in its function as a receptor organ for thermal stimuli, can influence the height of metabolism. Cold applied to the surface causes an increased production of heat in the body. When the external cold is removed, the basal metabolism returns to the normal level.

When cold was applied to the ligated extremity (chart 3), there was an increase in metabolism, but as soon as the ligature was removed, instead of a return to normal, the metabolic rate sank below the normal and did not return to the normal level until later. Helmreich explains this drop below the normal level by the theory that a mass of cold blood, withheld during ligation, rushes into the general circulation, depresses the temperature of the blood and thus causes a lowering of metabolism.

TABLE 2—Effect on Basal Metabolism of Ligating the Lower Extremities (Helmreich)

| Subject | Date | Part Ligated | Body Weight, Kg | Leg Weight, Kg * | Proportion of Body Weight, per Cent | Basal Metabolism, Ce Oxygen | Decrease During Ligation | Percentage Decrease |
|---------|--------|--------------|-----------------|------------------|-------------------------------------|-----------------------------|--------------------------|---------------------|
| A S | Feb 27 | Right leg | 74.3 | 10 | 13.5 | 312 | 30 | 8.7 |
| K G | Mar 1 | Left leg | 42 | 5.8 | 13.7 | 256 | 28 | 11.1 |
| | 1 | Right leg | | 5.73 | 13.5 | 260 | 33 | 12.6 |
| | 13 | Left leg | | | | 259 | 29 | 11.1 |
| | May 9 | Left leg | 45.3 | | | 305 | 38 | 12.5 |
| | 9 | Left leg | | | | 305 | 43 | 14 |
| | 19 | Both legs | 45.8 | 11.52 | 25.1 | 305 | 60 | 19.6 |
| R L | Mar 15 | Left leg | 33.6 | 4.35 | 12.8 | 221 | 30 | 13.5 |
| E S | Mar 17 | Right leg | 27.3 | 3.07 | 11.1 | 185 | 19 | 10.7 |
| H F | May 22 | Left leg | 39.9 | | | 238 | 26 | 10.8† |
| H W | May 17 | Left leg | 33.8 | | | 253 | 23 | 9 |

* Measured by volume of water displaced

† Herter's infantilism with large abdomen and thin legs

From our experience, we cannot recommend that this experiment be used with children as subjects. Ligating both extremities to the point of occlusion of the artery, and packing an extremity in ice is an unpleasant and even painful experience, and we needed to exercise self-control in order to lie quietly during the experimentation period.

The experiment does, however, furnish a way of bringing about an exclusion of blood from large parts of the body without creating, apparently, a pathologic state, and allows of comparison of metabolism before, during and after such exclusion.

Our results are in accord with those of Helmreich. This experiment was performed independently and in several ways more accurately than Helmreich's experiments. The periods of observation were longer, the subjects being adults instead of children, and the experiment was repeated frequently on the same person. The observations in themselves would seem to support the view taken by Helmreich that basal metabolism is independent of body surface, but is rather dependent on active

protoplasmic mass. The concordance with Helmreich's results might be construed to give further support to this idea.

Claim to originality is not made in the observations recorded. They are not submitted as conclusive. As far as they go, they seem to imply that basal metabolism does not have any causal relationship with body surface (Rubner), but rather depends on the amount of active protoplasmic tissue, varying with the mass of active cells, and the nervous stimulus to cellular activity existing at the time the test is made (Benedict).

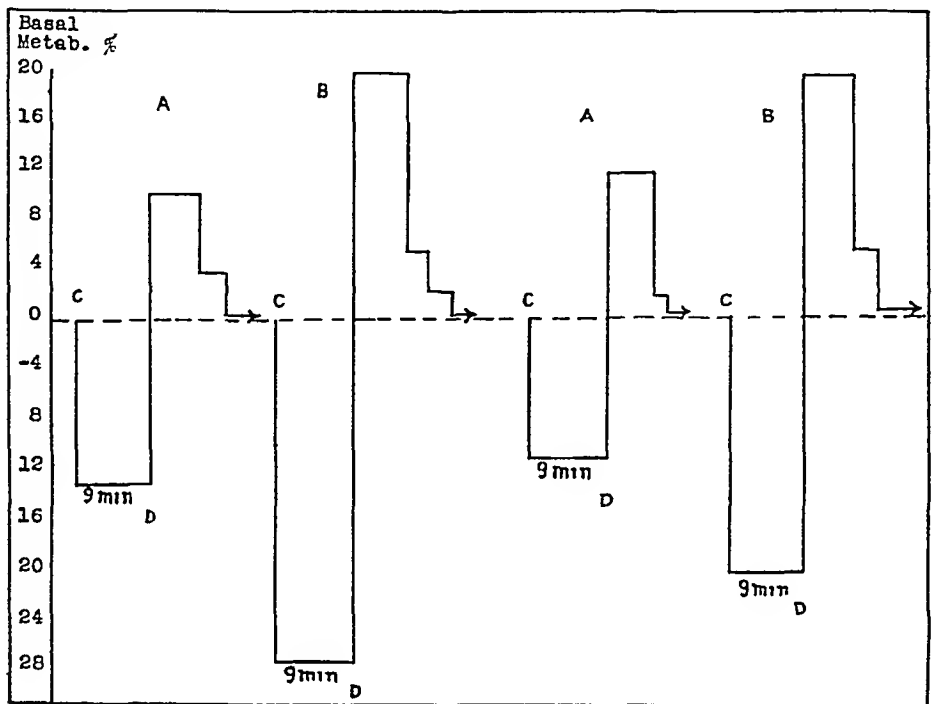


Chart 1—Effects of basal metabolism. The first two curves represent the experiments of Topper, and the second two represent those of Mulier. *A* indicates that one lower extremity was ligated, *B*, that both lower extremities were ligated, *C* indicates the point at which the ligature was applied, *D*, the point at which it was removed. The metabolism level is indicated by 0.

Body surface furnishes a biometric measurement which indicates, with approximate accuracy, the probable amount of active protoplasmic tissue in different persons. Body surface is a difficult surface to measure, involving the use of complicated formulas. To date, however, it seems to be the most practical single prediction standard for adults.

Talbot¹⁵ believes that the total metabolism for height will be the best single standard for children from 2 weeks to 12 years of age.

¹⁵ Talbot, F. B. Basal Metabolism of Children. *Physiol. Rev.* 5: 477 (Oct) 1925.

although he advises the use of all available standards in order to obtain a complete picture

All standards are used for comparison in our department but we find the Pirquet "sitting-height" standard the best single standard Pirquet, like Rubner, found a surface proportional to the nutritional needs of the body, but instead of using the outer surface, he looked for another surface which would be simpler to measure and which would also approximate the development and growth of the organism In studying

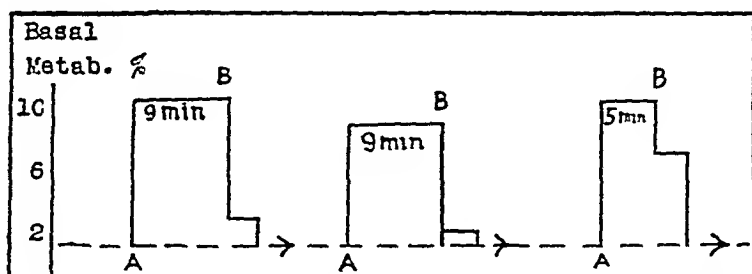


Chart 2—Effect on basal metabolism of the application of ice to extremity not ligated The first curve represents the experiments of Topper, the second those of Mulier, the third, those of Helmreich *A* indicates the point at which ice was applied *B* indicates the removal of the ice The metabolism level is indicated by 2

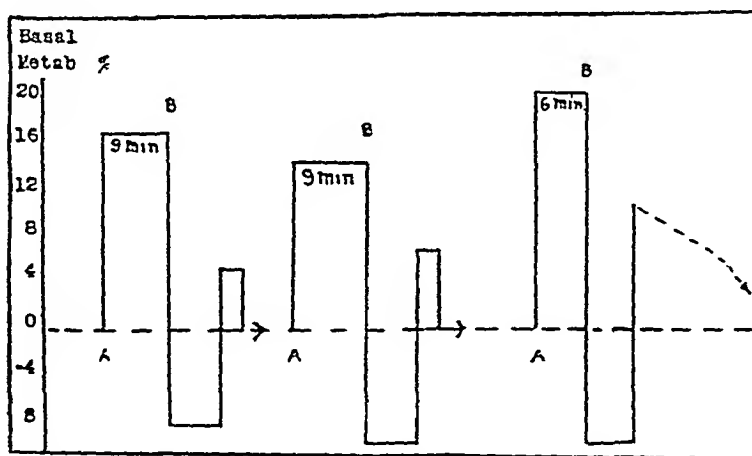


Chart 3—Effect on basal metabolism of application of ice to ligated extremity The first curve represents the experiments of Topper the second, those of Mulier, the third, those of Helmreich *A* indicates the point at which the ligature and the ice were applied, *B*, the point at which they were removed The metabolism level is indicated by 0

the relationship existing between the heart, pulse rate and body weight he discovered that the sitting height (height of the trunk) stands in close relationship to the cube root of the body weight and that this relationship remains constant throughout life The sitting height is easily measured with the simplest apparatus, and its application requires only

squaring instead of squaring and cubing, as do all other formulas for body surface. The minimal or basal metabolism corresponds to about three decimemsiqua, or translated into calories, 0.2 calory times si^2 equals basal metabolism. We find that this simple formula gives us the best single standard for basal metabolism, and it applies to adults as well as to children.

SUMMARY

In a series of experiments performed on ourselves, we found that when the lower extremities are cut off from the general circulation by ligation, the basal metabolism is decreased by an amount which roughly corresponds to the mass thus occluded and not to the surface area (table 1). When the ligature was removed, the level of the basal metabolism rose to normal.

If basal metabolism were dependent on body surface, the ligation of large parts of the body mass should not have any effect on the level of metabolism so long as the surface remains intact. That the surface remained intact in this case was proved by the fact that we reacted to tactile, pain and thermal stimuli applied to the ligated part (charts 2 and 3).

This work was a repetition of work originally done by Helmreich, and our observations are in accord with his observations.

Helmreich concludes from his experiment that basal metabolism is independent of body surface, but rather depends on the amount of active protoplasmic tissue.

It is not the purpose in this paper to discuss how far the results of our experiment and those of Helmreich's prove or disprove his conclusions. We realize that the problem is complex, and that further studies are necessary in order to decide the relation between basal metabolism and the active protoplasmic mass.

BASAL METABOLISM

I CORRELATION OF BASAL METABOLIC RATE AND BASAL PULSE RATE

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In 1920, Sturgis and Tompkins¹ reviewed the literature dealing with the relation between basal metabolism and resting pulse rate, and reported the results of their own study with special reference to hyperthyroidism. They found that a general parallelism existed between the basal metabolism and the pulse rate. In all but 16 per cent of 154 patients with hyperthyroidism, there was a tachycardia of 90 or more to the minute associated with a basal metabolism of $+15$ per cent or more. On the other hand, they found that during complete rest a pulse rate below 90 per minute is seldom found and that below 80 per minute is rarely associated with an increase in metabolism.

Minot and Means² found that the amount of elevation in the pulse rate for a given elevation in the metabolic rate is essentially the same in hyperthyroidism and in chronic leukemia, and they infer that in both diseases the tachycardia is chiefly the result of an increased metabolic rate. Thus, incidentally, their study tended to confirm the conclusions of Sturgis and Tompkins with reference to metabolism and pulse rates that were above normal.

In 1923 and again in 1926, the basal metabolism-basal pulse ratio was plotted in two series of unselected cases, with results similar to those of Sturgis and Tompkins. They are presented in charts 1 and 2 dated with their respective years. The fields are divided at 90 on the pulse rate scale (horizontal) and at $+20$ on the metabolic rate scale (vertical). The determinations of the metabolic rate are liable not only to the possibilities of error inherent in all methods of indirect calorimetry, but to an additional possibility of error of 1 per cent plus or minus involved in calculations by a logarithmic chart.³

The two charts here presented were plotted with reference to the correlation of metabolism and pulse rates in cases of hyperthyroidism, and the conclusions were in full accord with those already quoted from

1 Sturgis, C C, and Tompkins, E H. A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, *Arch Int Med* **26** 467 (Oct) 1920

2 Minot, G R, and Means, J H. The Metabolism-Pulse Ratio in Exophthalmic Goiter and in Leukemia, *Arch Int Med* **33** 576 (May) 1924

3 Smith, J H, and Smith, M C. *Boston M & S J* **186** 641 (May) 1922

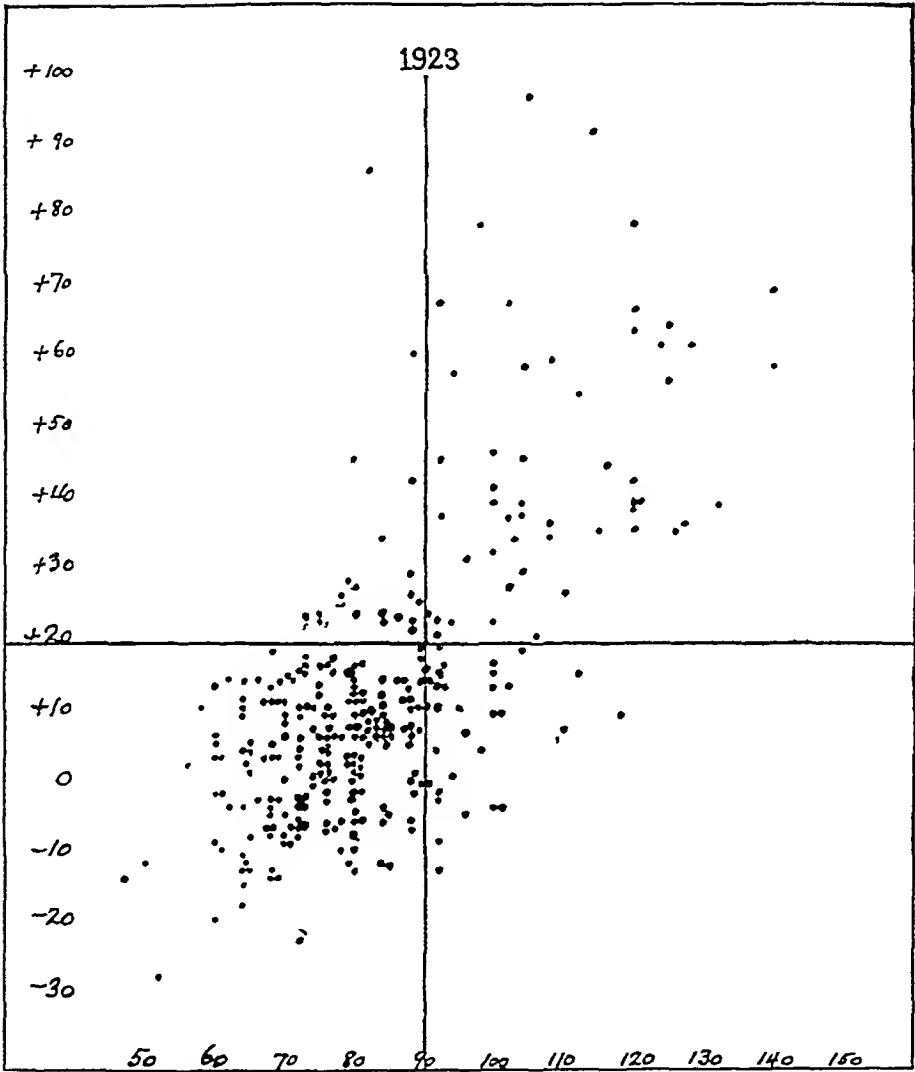


Chart 1—Basal metabolism—basal pulse ratio in a series of unselected cases in 1923

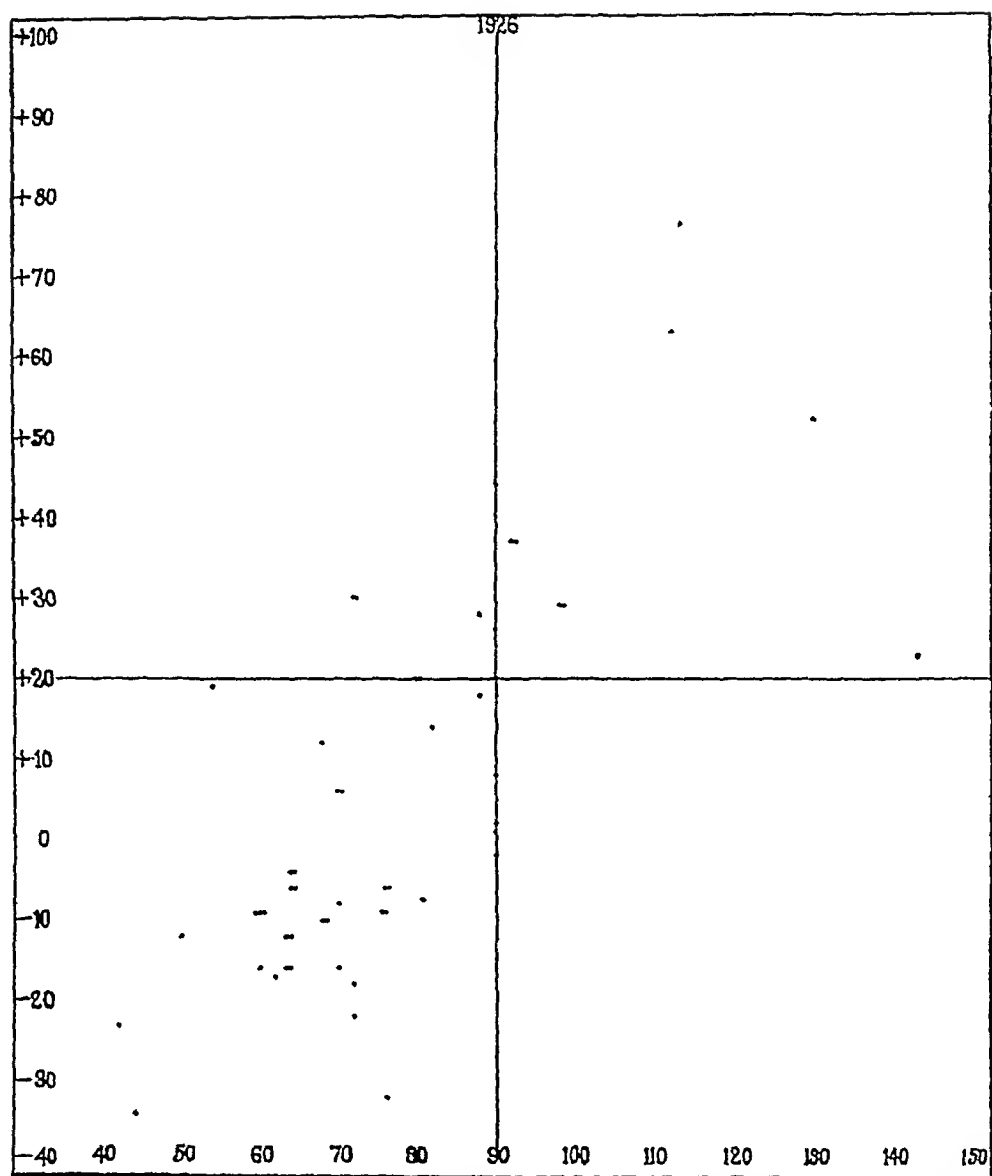


Chart 2—Basal metabolism—basal pulse ratio in a series of unselected cases in 1926

Sturgis and Tompkins The charts are shown, however, with the special object of emphasizing the value of the basal pulse rate as a control of the acceptability of metabolic determinations and as tending to justify the valuation put on the pulse rate in my next paper

It is obvious that the number of patients with a basal pulse rate of over 90 and a metabolic rate under ± 20 (southeast field in charts) is not of great importance, as the chances of error in normal or in low metabolic readings are not so great as in those above normal, and it is more usual to find tachycardia due to causes other than hyperthyroidism than to find hyperthyroidism in a patient with a normal or low pulse rate On the other hand, a basal metabolic rate of ± 20 or more with a basal pulse rate under 90 (northwest field) gives rise to some suspicion of the accuracy of the metabolic study, and often repetition of the test will give a lower reading, as it did in certain of the cases plotted in the northwest field of each chart

DETERMINATION OF CARDIAC HYPERTROPHY BY ROENTGEN-RAY METHODS *

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The differentiation of the enlarged heart from the heart of normal size is the most important single factor in determining the presence or absence of organic heart disease. With the exception of mitral stenosis and atrophic myocarditis, all but the rarest types of organic heart disease lead to hypertrophy of the ventricles. Except in rare instances, the left ventricle is most affected in the types with which the physician has to deal. This chamber is most affected in double mitral disease, in aortic disease, in adherent pericardium, in arterial hypertension and in myocardial degeneration associated with syphilitic or other types of aortitis and arterial injury. The greatly hypertrophied heart in advanced organic disease is easily recognized by the usual methods of physical examination, but there is need for more accurate differentiation of the hearts that are less abnormal and associated with an earlier stage in the pathologic process. This is the period when there is a possibility of retarding the advance of the condition, or, what is equally important, when persons with normal hearts who suspect or who have been told that they have organic heart disease can be given reassurance.

Studies in most of the lower animals (Hatai,¹ Pearce, Van Allen and Brown,² Josephs,³ Herrmann⁴) and in man (Boyd,⁵ Thoma,⁶ Muller,⁷ Beneke,⁸ Vierordt,⁹ Kress,¹⁰ Greenwood and Brown¹¹) have

* From the Department of Physiology, University of Wisconsin

1 Hatai, S. On the Influence of Exercise on the Growth of Organs in the Albino Rat, *Anat. Record* **9** 647, 1915

2 Brown, W. H., Pearce, Louise, and Van Allen, C. M. The Relation Between Body and Organ Weights in the Rabbit, *J. Exper. Med.* **44** 635, 1926

3 Josephs, D. R. The Ratio Between the Heart Weight and Body Weight in Various Animals, *J. Exper. Med.* **10** 521, 1908

4 Herrmann, G. R. Experimental Heart Disease, *Am. Heart J.* **1** 485, 1926

5 Boyd. Tables of the Weights of the Human Body and Internal Organs, *Philosophical Tr. Royal Soc. London* **151** 241, 1861

6 Thoma. Untersuchungen über die Grösse und des Gewicht der anatomischen Bestandtheile, Leipzig, 1882

7 Muller, W. Die Massenverhältnisse des menschlichen Herzens, Hamburg and Leipzig, 1883

8 Beneke, F. W. Die anatomischen Grundlagen der Constitutionen, Anomalien des Menschen, 1878

9 Vierordt. Daten und Tabellen, 1906

10 Kress, E. Ueber Organengewicht bei Kindern, Dissertation, Munich, 1902

11 Greenwood and Brown. A Study of the Weight, Variability and Correlation of the Human Viscera, *Biometrika* **9** 473, 1913

shown that the weight of the heart is more closely related to the size of the body than any other organ with the exception, perhaps of the brain. It is impossible, of course, to weigh the heart of a living being, and one is restricted to an estimation of its size or volume. This, however, is not a question merely of the muscle mass but of the amount of blood contained in the chambers of the organ, and this in turn varies with the particular phase of the cardiac cycle. Direct determination in the experimental animal (dog) indicates that the volume of blood in the heart in diastole is slightly less than that of the muscle of the heart (Bardeen¹²). Variations in the diastolic size of the heart may readily result from variations in the degree of cardiac filling, and it is possible to suppose that determination of the diastolic size in a given subject would be so variable as not to give a valid index of the true muscle mass. The modern conception of this phase of cardiodynamics is that the filling is primarily determined by systemic venous pressure, and there is reason to believe that under conditions of body rest it is fairly constant, although considerable increase may occur in muscular activity. The filling pressure even in cases of chronic heart disease is not increased unless decompensation occurs.¹³ Unless the changes in the heart rate are marked, they do not greatly alter the diastolic size (Meek¹⁴ and Hodges and Eyster¹⁵). The diastolic volume thus appears to be fairly constant in the same patient at different times when he is not in a state of muscular activity, and this conclusion is confirmed when repeated estimates are made on the same subject by roentgen-ray methods (Eyster and Evans,¹⁶ and Eyster, Meek and Hodges¹⁷). Assuming then that the mass of blood in the heart in diastole is a fairly constant factor under controlled conditions, variations in the heart volume should correspond closely to variations in the muscle mass. In valvular incompetence the increased ventricular output, however, makes probable the assumption of increased

12 Bardeen, C. R. Determination of the Size of the Heart by Means of the X-Rays. *Am J Anat* **23** 423, 1918.

13 Eyster, J. A. E. Venous Pressure and Its Clinical Applications, *Physiol Rev* **6** 281, 1926.

14 Meek, W. J. The Effect of Changes in Pulse Rate on Diastolic Heart Size, *Am J Physiol* **70** 385, 1924.

15 Hodges, P. C., and Eyster, J. A. E. Estimation of Cardiac Area in Man, *Am J Roentgenol* **12** 252, 1924.

16 Eyster, J. A. E., and Evans, J. S. Value of the X-Ray in Diagnosis of Chronic Valvular Heart Disease, *Tr A Am Phys*, 1923.

17 Eyster, J. A. E., Meek, W. J., and Hodges, F. J. Cardiac Changes Subsequent to Experimental Aortic Lesions. *Arch Int Med* **39** 536 (April) 1927.

diastolic filling, and a part of the enlargement that is found in such cases must be accredited to the increased mass of blood within the heart

An estimation of the cardiac size in man can be made only indirectly by the projection of one or more of the surface planes of the heart. Two general methods have been employed for this purpose—topographic percussion and the roentgen-ray projection. It is generally agreed that the latter is more objective and accurate. In order to avoid the distortion and enlargement of the silhouette in roentgen-ray projection, two methods have been employed—teleroentgenography and orthodiagraphy. In the former the film is placed as close to the heart as possible, and the source of the divergent roentgen rays, the target of the tube, is placed sufficiently far away to give approximately parallel rays. The usual working distance is 2 meters or approximately 7 feet, and under these conditions the enlargement of the silhouette as compared to the plane of the heart is approximately 3 per cent in linear dimensions. In orthodiagraphy, the principle of orthographic projection first applied by Moritz,¹⁸ in which only the central or incident bundle of rays is used to form the projection, a silhouette of the same size as the plane of the object casting the shadow is secured by parallel ray projection. If the heart were a sphere, its volume could be calculated from the area of its projection in any plane.¹⁹ This, however, is not the case, and the estimation of volume from one plane surface can be only an approximation. Theoretically, if projections of plane surface were obtained from a number of different views, the heart as a solid body could be reconstructed by orthographic projection, and its volume could thus be accurately determined, but practically, such reconstruction is difficult or impossible in man due to the interference of other structures with the shadow cast by the heart, structures such as the sternum, vertebral column, diaphragm and liver and by the great vessels at the base of the heart. Bardeen,¹² however, has shown by direct determination of the volume of the heart in cadavers that a fair approximation can be obtained from a single plane (the frontal), and Skavlem²⁰ has confirmed this on the dog.²¹ From

18 Moritz, F. Eine Methode um beim Röntgenverfahren aus dem Schattenbilde eines Gegenstandes dessen wahre Grösse zu ermitteln (Orthodiagraphie) und die exakte Bestimmung des Herzgrösse nach diesem Verfahren, München Med. Wchnschr. **47** 992, 1900.

19 $\text{Volume} = \text{Plane area}^{3/2} \frac{4}{3\sqrt{\pi}}$

20 Skavlem, J. H. Estimation of Cardiac Volume in the Living Animal by Means of the Teleroentgenogram, Am. J. Physiol. **61** 501, 1922.

21 The formula for the human heart is, $\text{volume} = 0.53 A^{3/2}$ and for the dog's heart, $\text{volume} = 0.44 A^{3/2}$ when A equals the area of the silhouette of the frontal plane.

the standpoint of the clinical goal of separation of the hypertrophied from the normal heart such determination of volume is not essential if some other measurement or system of measurements is sufficient to ensure this separation. The real criterion of the value of any method of cardiac mensuration is its effectiveness in arriving at this differentiation.

REVIEW OF LITERATURE

Since the time of Moritz's first publication, numerous workers have attempted to establish normal standards for measurements applied to the silhouette of the frontal plane obtained by orthodiagraphy or teleroentgenography. Moritz²² proposed a rather complicated system of vertical, longitudinal and transverse diameter measurements, and these were applied, with the addition of surface area of the silhouette by Dietlen,²³ in a large series of normal subjects. Other more or less extensive studies in normal subjects have been made by Groedel,²⁴ Clayton and Merrill,²⁵ Otten,²⁶ Williamson,²⁷ Shattuck,²⁸ Bardeen,¹² Haudek,²⁹ Bertnard Smith,³⁰ H. E. Smith and Bloedern³¹ and Cohn.³² In these studies efforts have been made to relate the measurements found with certain body measurements, especially in height and weight, and with age, sex and body conformation. There has also been a tendency to reduce the number of silhouette measurements and to emphasize the value of two, the area of the frontal plane and the greatest transverse diameter of the silhouette of the frontal plane. The former appears to have the advantage of combining the elements of the various

22 Moritz, F. Ueber orthodiagraphische untersuchungen am Herzen, *Munchen Med Wchnschr* **49** 1, 1902

23 Dietlen. Ueber Grosse und Lage des normalen Herzens und ihre Abhangigkeit von physiologischen Bedingungen, *Deutsches Arch f klin Med* **88** 54, 1907

24 Groedel, F. M. Die Rontgendiagnostik der Herz und gefasser Erkrankungen, Berlin, 1912

25 Clayton, T. A., and Merrill, W. H. Orthodiagraphy in the Study of the Heart and Great Vessels, *Am J M Sc* **138** 549, 1909

26 Otten, M. Die Bedeutung der Orthodiagraphie fur die Erkennung des beginnenden Herzweiterung, *Deutsches Arch f klin Med* **105** 370, 1911

27 Williamson, C. S. The Effects of Exercise on the Normal and Pathological Heart, *Am J M Sc* **138** 549, 1909

28 Shattuck, G. C. How Can We Detect Slight Enlargement of the Heart? *Boston M S J* **174** 385, 1916

29 Haudek, M. Rontgenologie—Eine Revision der Methodik der rontgenologischen Herzgrosssenbeurteilung, *Jahreskurse fur arztliche Fortbildung*, 1918

30 Smith, B. Teleroentgen Measurements of the Hearts of Normal Soldiers, *Arch Int Med* **25** 522 (May) 1920

31 Smith, H. E., and Bloedern, W. A. *U S Nav M Bull* **16** 219, 1922

32 Cohn, A. E. An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method, *Arch Int Med* **25** 499 (May) 1920

diameter measurements and to be less subject to variation from minor influences, but it has the disadvantage that it requires arbitrary completion of the upper border of the cardiac shadow when it merges with the great vessels and of the lower border when it is contiguous with the diaphragm. This difficulty is much greater in teleroentgenography than in orthodiagraphy, and it is impossible to make satisfactory measurements in many teleroentgenograms in subjects with a short thorax and a high diaphragm. A much more accurate completion of the lower border can be obtained by orthodiagraphy, because of the possibility of separating two shadows of approximately equal density (heart and diaphragm) by taking advantage of their differences in movement (Eyster³³). Completion of the border contiguous to the greater vessels is also more accurate when done orthodiagraphically, because of the possibility of the location of the junction of the right auricle and the vena cava on the right contour and of the left auricle and left ventricle on the left contour of the heart. The greatest transverse diameter of the silhouette of the frontal plane has the advantage of being the most objective and definite measurement that can be applied to this silhouette. It, however, appears to be more variable as a result of minor influences such as the extent of the stomach filling and the phase of respiration. All measurements of the silhouette of the heart, so far as I know, have been confined to the frontal plane, although observations on the extent of the retrocardiac space (space between the posterior border of the heart and the vertebral column) in the lateral plane have been recorded by Vaquet and Bordet³⁴ and by Eyster and Evans¹⁶ and Eyster³³.

P. C. Hodges and Eyster¹⁵ and F. J. Hodges and Eyster³⁵ published prediction tables for the size of the normal heart based on surface area and transverse diameter of the orthodiagraphic silhouette of the frontal plane in which the variables of age, height and weight were subjected to mathematical analysis. The subjects represented a group of normal persons selected after careful clinical examination. By this method it was possible to evaluate the different variables and to give them proper weight in the regression equation on which the prediction tables were based, and thus to assure, it was believed, a more accurate prediction than that found in tables previously published. The true evaluation, however, of a method such as this is its ability to separate

33 Eyster, J. A. E. *The Size of the Heart in the Normal and in Organic Heart Disease*, Radiology, 1927.

34 Vaquez, H., and Bordet, E. *The Heart and the Aorta*, English translation by J. A. Honeji, New Haven, 1920.

35 Hodges, F. J., and Eyster, J. A. E. *Estimation of Transverse Cardiac Diameter in Man*, Arch Int Med 37 707 (May) 1926.

the normal from the enlarged heart, and in order to test this I applied the method in a study of 424 cases of normal and chronic heart disease³ It was found that subjects with organic heart disease of types that were known to be associated with hypertrophy were differentiated with a degree of accuracy that would lead to the conclusion that the method was of distinct clinical importance In cases of mitral and aortic disease, selected as characteristic of the earlier stages of the lesion before signs or symptoms of cardiac failure had occurred, a distribution above the upper normal range of 84 per cent of all cases was shown Ninety-four per cent were more than 10 per cent above the predicted normal area while in the normal series of cases only 9 per cent of all cases exceeded the prediction by more than 10 per cent Similar but less marked separation could be made on the basis of the greatest transverse diameter

METHODS

The present study is concerned with an attempt to evaluate the introduction of other measurements of orthodiagraphic silhouettes and of other body measurements in relation to the prediction of the size of the normal heart and the separation of normal and hypertrophic hearts The measurements of the silhouettes studied were the area and greatest transverse diameter of the silhouette of the lateral plane combined with similar measurements from the frontal plane The additional body measurements introduced were the anteroposterior and lateral diameters and the girth of the thorax (made at the third intercostal space) A new series of 100 carefully selected normal persons was studied and compared with 100 patients with organic heart disease, the latter group comprised 55 cases of mitral stenosis and regurgitation, 25 cases of aortic regurgitation, 10 cases of aortic and mitral disease, 15 cases of hypertension with clinical signs of cardiac hypertrophy and 5 cases with clinical signs of adherent pericardium In all of these cases the compensation of the heart was good, and the history did not suggest cardiac failure The data from the normal series were submitted to mathematical analysis, and regression equations were determined for prediction, the new silhouette and body measurements being used The data, including thoracic measurements, are restricted to fifty cases in each group In the mathematical treatment of these data it became evident that the best prediction combination of the four cardiac measurements the areas of the frontal and lateral planes and the transverse diameters of the frontal and lateral planes, was the sum of the two transverse diameters, and that the addition of the areas contributed too little to justify their inclusion in the final formula

New formulas were also developed for the area of the frontal plane and transverse diameter including the thoracic measurements in addition to age height and weight as variables

With the new prediction tables available, the next step was to test the degree of separation of the normal and pathologic by plotting the results of each group on distribution curves. In these curves, the results in cases corresponding with the prediction are plotted as showing zero variation, and those of other cases are plotted according to whether they vary in percentage from the prediction above (+) or below (—). The extent of overlapping of the normal and pathologic, the range between an arbitrary percentage variation from the predicted (± 10 per cent) and the percentage of pathologic cases exceeding the upper normal range are shown. Three additional simple ratios available from the data are included, these concern the relation between the transverse diameter and the area of the silhouette of the frontal plane and the thoracic measurements.

MATHEMATICAL TREATMENT

An attempt to discuss the statistical theory in detail on which the mathematical treatment of the present material is based would be out of place in the present communication, and it must suffice to refer to the writings of Thorndike,³⁶ Pearson,³⁷ Yule³⁸ and Hull,³⁹ to its application to biologic study by Harris and Benedict⁴⁰ and to its previous application to cardiac mensuration by Hodges and Eyster.⁴¹

The method depends on obtaining partial and multiple coefficients of correlation and in giving to each variable a weight that will produce the highest degree of correlation between the variables and the criterion. In the first study, that in which measurements from the silhouettes of both the frontal and the lateral planes were employed, there were four criteria: the area of the frontal plane, the transverse diameter of the frontal plane, the area of the lateral plane and the transverse diameter of the lateral plane. The variables were age, height or stature, and weight. In the second mathematical treatment of the material, thoracic measurements were also introduced as variables. In addition to the four basic measurements of the heart, treated separately, various combinations were tested as follows: the sum of the areas of the frontal and lateral planes, the sum of the transverse diameters of the frontal and lateral planes, the product of the transverse diameter of the frontal plane by the area of the lateral plane and the product of the transverse diameter of the lateral plane by the area of the frontal plane. All possible intercoefficients of correlation were first com-

36 Thorndike, E. L. *An Introduction to the Theory of Mental and Social Measurements*, Columbia University Press.

37 Pearson, Karl. *Tables for Statisticians and Biometricians*, Cambridge University Press, 1914.

38 Yule, G. U. *An Introduction to the Theory of Statistics*, London, Charles Griffin, 1919.

39 Hull, C. L. *Prediction Formulae for Teams of Aptitude Tests*, *Applied Psychology* 7: 277, 1923.

40 Harris, J. A., and Benedict, F. G. *A biometric Study of Basal Metabolism in Man*, Carnegie Institute, Washington, 1919.

41 Hodges, P. C., and Eyster, J. A. E. (footnote 15) and Eyster, J. A. E. (footnote 33).

puted as well as the mean and standard deviations, the correlating machine devised by Hull being used and checked to absolute accuracy. The formula used for obtaining the simple coefficients of correlation was

$$r = \frac{M_1X_2 - M_1XM_2}{\sqrt{M_1^2 - (M_1)^2} \sqrt{M_2^2 - (M_2)^2}}$$

The multiple coefficients of correlation were obtained by the formula

$$R_{0, 1, 2, 3} = \frac{W_1P_{01} + W_2P_{02} + W_3P_{03}}{P_{00}}$$

In table 1 is given the multiple coefficients of correlation for the various combinations of the heart and body measurements. These figures express the extent of correlation or agreement between these measurements and give an

TABLE 1—*Multiple Coefficients of Correlation for Various Combinations of Heart and Body Measurements*

| Heart Measurements | Age, Height, Weight | Age, Height, Weight and Thoracic Measurements |
|--|---------------------|---|
| Area of frontal plane | 0.547 | 0.575 |
| Transverse diameter of frontal plane | 0.693 | 0.681 |
| Area of lateral plane | 0.454 | 0.444 |
| Transverse diameter of lateral plane | 0.499 | 0.598 |
| Sum of areas of lateral and frontal planes | 0.631 | 0.635 |
| Sum of transverse diameters of lateral and frontal planes | 0.700 | 0.734 |
| Area of frontal and transverse diameter of lateral plane | 0.616 | 0.622 |
| Transverse diameter of frontal plane and area of lateral plane | 0.654 | 0.671 |

index of the accuracy of prediction that it is possible to make. The prediction formulas developed were as follows:

1. Formula for the sum of the transverse diameters of the frontal and lateral planes based on age, height and weight

$$X_0 = 0.28542 \times \text{age} - 0.489355 \times \text{height} + 1.34498 \times \text{weight} + 185.84$$

2. Formula for the sum of the transverse diameters of the frontal and lateral planes based on age, height, weight and thoracic measurements

$$X_0 = -0.19175 \times \text{age} - 1.17373 \times \text{height} + 1.10799 \times \text{weight} - 0.07063 \times \text{anteroposterior diameter} + 0.07835 \times \text{lateral diameter} + 0.75981 \times \text{girth} + 260.306$$

3. Formula for the area of the frontal plane based on age, height, weight and thoracic measurements

$$X_0 = -0.61315 \times \text{age} + 0.050378 \times \text{height} + 0.578655 \times \text{weight} - 0.18051 \times \text{anteroposterior diameter} + 0.160057 \times \text{lateral diameter} - 0.2876 \times \text{girth} + 81.18$$

4. Formula for the transverse diameter of the frontal plane based on age, height, weight and thoracic measurements

$$X_0 = -0.05932 \times \text{age} - 0.914298 \times \text{height} + 0.959396 \times \text{weight} - 0.20951 \times \text{anteroposterior diameter} + 0.0256 \times \text{lateral diameter} + 0.49855 \times \text{girth} + 208.2$$

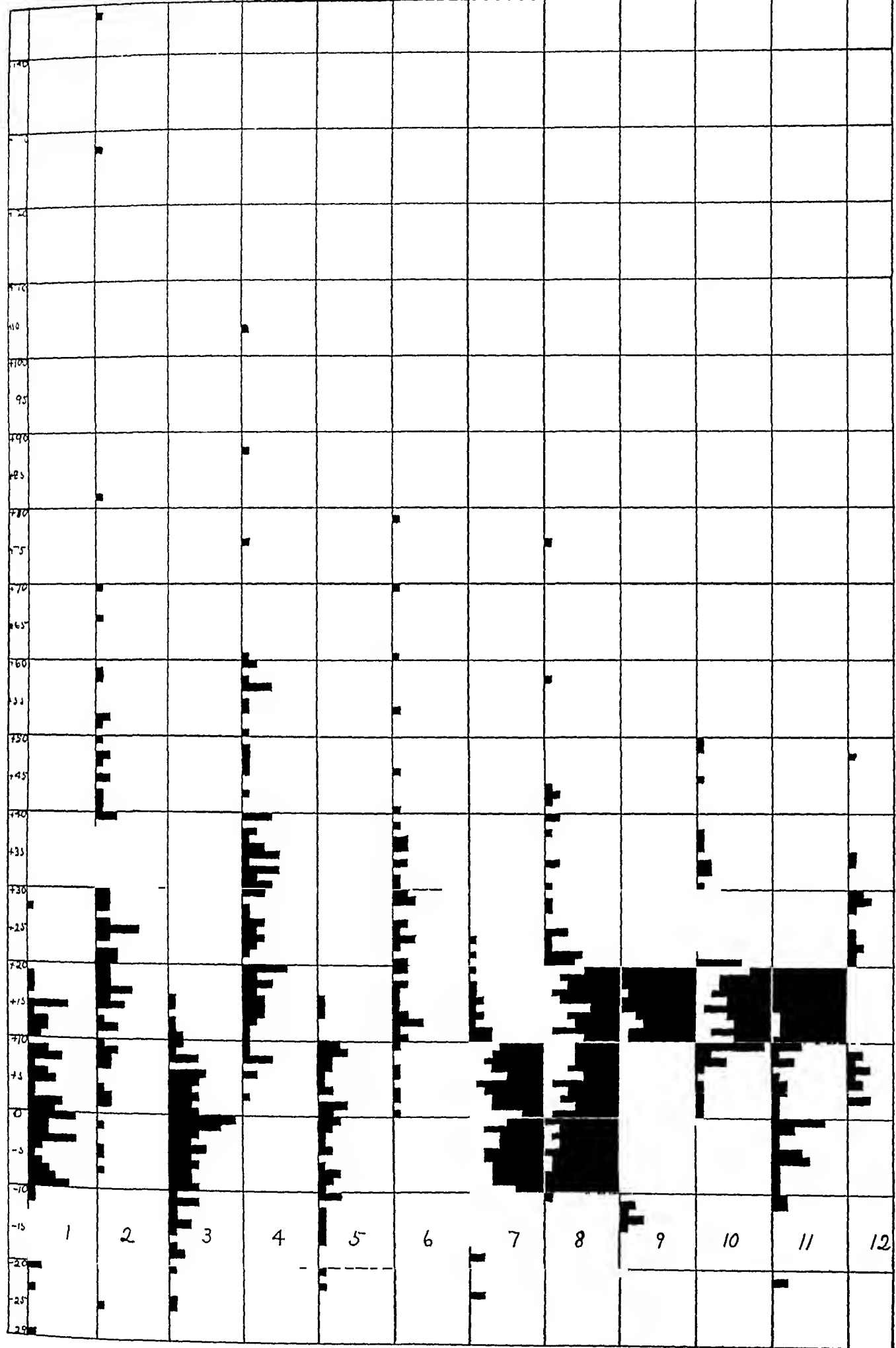


Chart 1—Distribution of measurements from frontal and lateral orthodiagrams in normal cases and in cases of organic heart disease

RESULTS OF STUDY

The results of this study are given in the form of distribution curves in charts 1 and 2. With the exception of the four last columns in chart 2 (from 17 to 20 inclusive), the results of each are charted in regard to their variation in percentage from the predicted. In columns 1 and 2 and in 7 and 8, concerned with the area and transverse diameter of the frontal plane respectively, prediction was based on the arithmetical means of the normal series. These means were 112

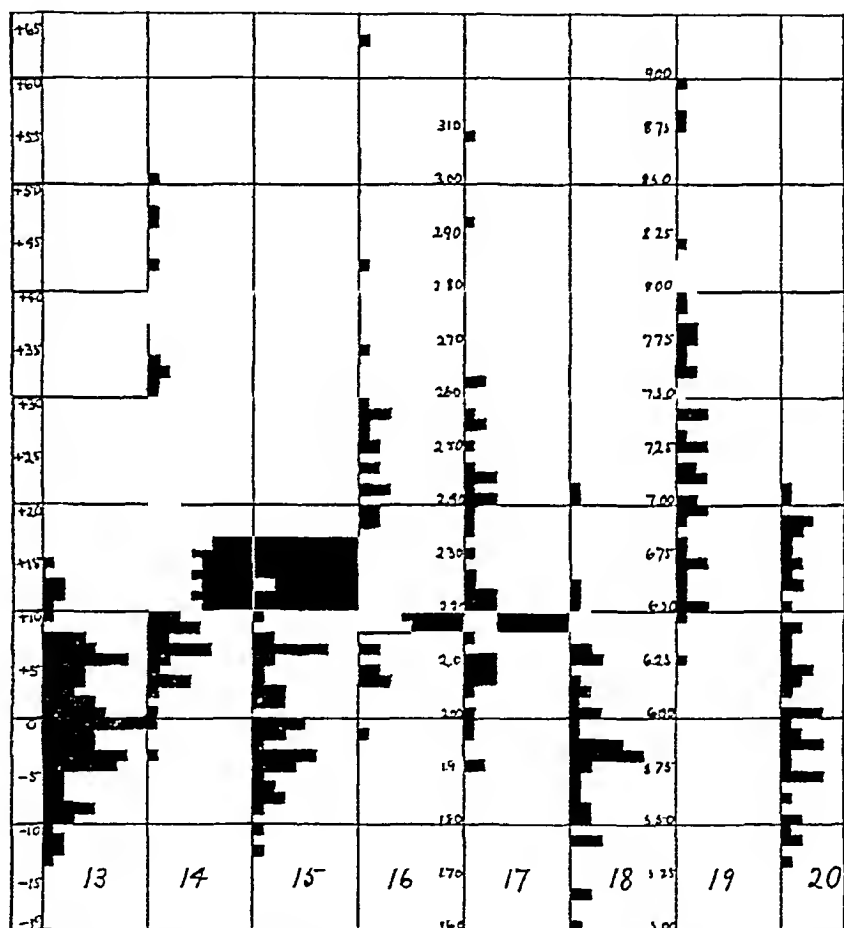


Chart 2—Distribution of measurements from frontal and lateral orthodiagrams in normal cases and in cases of organic heart disease

sq cm in the area of the frontal plane and 124 mm in the transverse diameter of the frontal plane. In all the other columns (except columns 17 to 20) prediction was based on one of the formulas developed in this or in previous work (Hodges and Eyster⁴¹). In the last four columns of chart 2, the results are charted as actual measurements.

In columns 1 to 6 inclusive, the areas of the frontal plane are considered. Column 1 represents the distribution of 100 normal subjects in which the areas of the frontal plane are charted according to their

variation from the arithmetical mean of the group (112 sq cm) Column 2 represents the distribution of 100 cases of organic heart disease from the normal mean Columns 3 and 4 represent similar considerations of the normal and abnormal groups in which prediction was based on the formula, age, height and weight being used as variables (Hodges and Eyster¹⁵), and columns 5 and 6 comprise fifty cases in each group in which the additional variables of thoracic measurements were introduced and predicted according to formula 3 Columns from 7 to 12, inclusive, represent an exactly similar series in which the determination of the transverse diameter of the frontal plane was made Column 7 represents the normal series based on the arithmetical mean (124 mm), and column 8 the abnormal group similarly predicted Column 9 represents the normal group in which prediction was made by the formula, age, height and weight previously published (Hodges and Eyster¹⁵) being employed, column 10 similar treatment of the abnormal group, and columns 11 and 12 groups of fifty cases each from the normal and abnormal groups, thoracic measurements being used as additional variables in the prediction according to formula 4

The first four columns of chart 2 represent the application of the additional cardiac measurements from the silhouette of the lateral plane Consideration of the area and transverse diameter of the lateral plane alone and in combination with measurements of the frontal plane indicated that the best prediction would be obtained by employing the sum of the two diameters, the frontal and the lateral (table 1) Inclusion of area measurements complicated the procedure without improving it Accurate delineation of the contour in its upper and lower boundaries is more difficult in the lateral than in the frontal plane owing to the greater density of the shadows cast by the diaphragm and the interposition of the hila of the lungs The anterior and the posterior contour, so long as the latter is clear from the shadow of the spinal column are, however, readily obtained with accurate measurement of the greatest transverse diameter Formulas were developed to predict the sum of the two transverse diameters, age, height and weight being used as variables (formula 1) and the introduction of thoracic measurements as additional variables (formula 2) Column 13 (chart 2) shows the distribution from the predicted of the same group of 100 normal cases, and column 14 shows the same group of 100 pathologic cases previously employed in the other types of measurement, height and weight being used as variables (formula 1) Columns 15 and 16 show results in fifty cases in each of the normal and pathologic series in which thoracic measurements were available and which were predicted by formula 2

Columns 17 to 20, inclusive, represent simple ratios between the transverse diameter of the silhouette of the frontal plane and

the transverse diameter and girth of the thorax, respectively. As there is no normal prediction in these, they are plotted, not as variations in percentage, but as the actual ratio. In column 17, the results from the ratio $\frac{\text{Transverse Diameter of the Thorax}}{\text{Frontal Transverse Diameter of the Heart}}$ of fifty normal subjects are plotted, and column 18 represents the same from fifty subjects with organic heart disease. Column 19 records the ratio $\frac{\text{Girth of the Thorax}}{\text{Frontal Transverse Diameter of the Heart}}$ in the same series of normal subjects and column 20 in the same series of pathologic cases.

COMMENT

The real criterion for the value of any method applied in clinical diagnosis is its ability to separate the normal and pathologic cases. Considered in this light it appears obvious that the area and transverse diameter of the frontal plane, predicted from age, height and weight, are of definite value, and that little if anything is gained by the introduction of other cardiac or body measurements (thoracic). Measurements from the silhouette of the lateral plane appear to improve slightly the prediction in normal cases (comparison of column 13 with columns 3 and 9), but the separation from the pathologic is less. The probable reason for this is that the true measurement of the transverse diameter of the silhouette of the lateral plane is not obtained in enlargement of the left ventricle, because the posterior cardiac contour is displaced dorsally and fuses with the shadow of the spinal column resulting in an obliteration of the retrocardiac space. This measurement, which it is possible to make accurately in the normal subject, thus is probably underestimated in most of the pathologic cases.

Three ratios between measurements from the silhouette of the frontal plane and thoracic measurements have also been considered. The first of these, the ratio between the greatest transverse diameter of the heart and the transverse diameter of the thorax (columns 18 and 19, chart 2) has been advocated by Kreufuchs⁴² and by Danzer⁴³. It is the method for attempting to distinguish hypertrophied hearts which has been most widely used in this country. According to Danzer, the width of the heart forms from 39 to 50 per cent of the width of the thorax in normal subjects. If the diameter of the heart is more than half the diameter of the thorax, the possibility of hypertrophy should be considered, and if the percentage of the diameter of the heart rises to 53 per cent or more, hypertrophy is definitely present. In hearts of the "drop" type, of small initial transverse diameter, consider-

42 Kreufuchs. Eine neues Verfahren des Herzmessung, Munchen Med Wchnshcr **59** 1030, 1912

43 Danzer, C. S. The Cardio-Thoracic Ratio, an Index of Cardiac Enlargement, Am J M Sc **157** 513, 1919

able hypertrophy may develop, however, without the ratio exceeding the normal range, and Danzer's final conclusion is that if the cardio-thoracic ratio exceeds the normal range, hypertrophy is constituted, if not the possibility of hypertrophy cannot be ruled out. It is evident from a consideration of this method in the present series of cases that it has little clinical value. It is, in fact, little better than assuming an average transverse diameter as the basis for prediction, and it gives a distinctly poorer prediction than any of the methods using the area of the frontal plane, including the one based on average values. Distinctly better separation of normal and hypertrophied hearts is obtained by employing the thoracic girth in the ratio instead of the transverse diameter of the thorax (columns 19 and 20, chart 2), and an even better ratio is that between the cardiac area of the frontal plane and the thoracic girth (table 2). The latter, however, involves measurement of the area of the plane and does not have any advantage over the prediction based on age, height and weight. It does, however, emphasize the fact that the area of the silhouette of the frontal plane is a more valuable measurement than the transverse diameter and more neatly approximates a determination of the true size of the heart. In the present series of normal subjects, the transverse diameter of the heart was less than half the transverse diameter of the thorax in 94 per cent, but this was also true in 38 per cent of the pathologic cases, and only 42 per cent of the latter equaled or exceeded Danzer's upper range of 52 per cent.

In order to show more clearly the value of the different methods considered, certain points are included in table 2. The first column gives the type of measurement employed, and the succeeding four columns the percentage of cases lying between ± 10 and above $+ 10$ per cent in the normal and pathologic series. The sixth column gives the percentage of the pathologic cases that exceed the upper range of the normal. In an effort to evaluate the separation of the normal and pathologic cases, the seventh column is included in which the figures represent the percentage above $+ 10$ per cent in the normal subtracted from the percentage above $+ 10$ per cent in the pathologic as a measure of the extent of overlapping beyond what may be considered as a fair upper normal variation. To give a final figure representing the order of value of the different methods, the eighth column gives the sum of the two preceding columns. It is obvious that the determination of the area of the frontal plane is the most important single cardiac measurement, and that little if anything is gained by inclusion of other cardiac or of body measurements in addition to those of height and weight. In a preceding paper³⁵ it has been pointed out that possibly a gain would be made in accuracy of prediction of the size of the heart by including other

TABLE 2—Comparison of Different Methods for Predicting Orthodiagraphic Measurements of the Heart

| Type of Measurement | Normal | | | Pathologic Cases | | | Percentage Above +10 in Normal Subjects Subtracted from Percentage Above +10 in Pathologic Cases | Addition of Last Two Columns | Order of Value | Columns in Charts 1 and 2 |
|--|--------------------|---------------|--|--------------------|---------------|--------------------------|--|------------------------------|----------------|---------------------------|
| | Between $\pm 10\%$ | Above $+10\%$ | | Between $\pm 10\%$ | Above $+10\%$ | Above Upper Normal Range | | | | |
| Area of frontal plane, based on average, no prediction | 66 | 19 | | 17 | 82 | 43 | 63 | 106 | 9 | 1 and 2 |
| Area of frontal plane, prediction based on age, height, weight | 78 | 6 | | 9 | 91 | 78 | 85 | 163 | 1 | 3 and 4 |
| Area of frontal plane, prediction based on age, height, weight and thoracic measurements | 80 | 6 | | 12 | 88 | 66 | 82 | 118 | 2 | 5 and 6 |
| Transverse diameter of frontal plane, no prediction, based on average | 70 | 17 | | 39 | 60 | 17 | 48 | 60 | 11 | 7 and 8 |
| Transverse diameter of frontal plane, prediction based on age, height, weight | 84 | 8 | | 22 | 78 | 55 | 70 | 125 | 5 | 9 and 10 |
| Transverse diameter of frontal plane, prediction based on age, height, weight and thoracic measurements | 89 | 6 | | 24 | 76 | 60 | 70 | 130 | 4 | 11 and 12 |
| Sum of transverse diameters of frontal and lateral planes, prediction based on age, height, weight | 89 | 6 | | 27 | 73 | 49 | 67 | 116 | 7 | 13 and 14 |
| Sum of transverse diameters of frontal and lateral planes, prediction based on age, height, weight and thoracic measurements | 91 | 1 | | 34 | 66 | 70 | 62 | 112 | 8 | 15 and 16 |
| Transverse diameter of thorax | | | | | | | | | | |
| Transverse diameter of heart | 74* | 10† | | 36 | 64† | 26 | 54 | 80 | 10 | 17 and 18 |
| Girth of thorax | | | | | | | | | | |
| Transverse diameter of heart | 78* | 12† | | 28 | 72† | 60 | 60 | 120 | 6 | 19 and 20 |
| Girth of thorax | | | | | | | | | | |
| Area of frontal plane | 62* | 20† | | 6 | 94† | 62 | 74 | 136 | 3 | |

The asterisk indicates \pm is referred to average and the dagger indicates below -10 per cent

body measurements, but if so these should be such as would correlate more closely with the size of the heart than with the body measurements already employed. It was shown, for example, that sitting height correlates so closely with standing height that either may be employed but that there is no advantage in using both. It appears probable that a type of body measurement will not be found which correlates better with the size of the heart than height and weight, unless perhaps it is some other organ weight obviously impossible of clinical use. Inclusion of other measurements thus introduces complications without corresponding improvement in the accuracy of prediction.

Considerable criticism has been directed to the use of the area of the frontal plane because of the necessity of the arbitrary completion of portions of the cardiac contour, and it has been regarded as so inaccurate and subjective in nature as to lead to its rejection by certain recent workers (Deutsch and Kauf⁴⁴). My rather long experience with this method has led to the conviction that it is accurate if measured from the orthodiagraphic tracing made by one with some experience in this type of work. Repeated determinations on the same person and comparison of orthodiagrams made by different observers confirm this view. On the other hand, it is most inaccurate when an attempt is made to apply it to many teleroentgenograms, and if used at all with them, it should be applied only in selected cases in which the heart lies relatively free from the diaphragmatic shadow. If one must work with teleroentgenograms, it is preferable to rely on the greatest transverse diameter which is accurately obtained and predicted according to the formula previously published (Hodges and Eyster³⁵) or perhaps by employing the ratio of the thoracic girth as the present work suggests. Orthodiagraphy should be employed whenever possible, not only because it leads to more accurate mensuration, but because it also allows a fluoroscopic examination of the great vessels, and observation in the lateral and in the various oblique planes when desirable. In my opinion the roentgen ray is as valuable in the diagnosis of cardiovascular diseases as it is in gastro-enterology, and it is far more comprehensive in the information it supplies than any of the other adjuncts of clinical study.

CONCLUSIONS

1. A comparison of the area of the orthodiagram of the frontal plane with the predicted area using age, height and weight as variables affords the best separation so far employed in differentiating between normal and hypertrophic hearts.

⁴⁴ Deutsch, F., and Kauf, E. *Heart and Athletics*, English translation by L. M. Warfield, St. Louis, C. V. Mosby Company, 1927.

2 The introduction of other body (thoracic) and heart measurements from other planes results in little if any gain in accuracy

3 The transverse diameter of the silhouette of the frontal plane (orthodiagraphic or teleroentgenographic) similarly predicted or determined from the ratio $\frac{\text{Thoracic Girth}}{\text{Transverse Diameter of the Heart}}$ represents what appears to be the next most valuable method for differentiation

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ROENTGEN-RAY TREATMENT OF THE SPLEEN IN ASTHMA AND IN RELATED ALLERGIC DISEASES *

GEORGE L WALDBOTT, M D

DETROIT

In 1920, Drey and Lossen¹ treated a patient who was afflicted simultaneously with leukemia and bronchial asthma by irradiation of the spleen with the roentgen ray, they noticed that the asthmatic condition improved appreciably. Similar reports of the recovery of asthmatic patients following irradiation administered to alleviate other ailments are given by Scott² and Schilling³. In 1925, Groedel⁴ treated a number of asthmatic patients by irradiation of the spleen and was favorably impressed with the results. Others (Pohlmann,⁵ Gallino and Terrada⁶ and Moner⁷) concurred in the optimistic opinions of the foregoing authors on the value of this form of therapy.

In this country, Geiber⁸ introduced this procedure for the treatment of patients with asthma, and at the same time advocated exposure of the chest, the so-called direct method, which is based on the previous work of Klewitz,⁹ Schilling³ and others.

*From the Asthma Clinics of the Children's Hospital of Michigan and the North End Clinic

1 Drey, L., and Lossen, H. Beseitigung chronischen Bronchialasthmas durch Fernwirkung der Roentgenstrahlen bei Milzbestrahlung, *Strahlentherapie* **19** 1052, 1920

2 Scott, G. Method of Treating Asthma by Radiation, *Brit M J* **1** 9 (June) 1926

3 Schilling, T. Gunstige Beeinflussung der chronischen Bronchitis durch Roentgenstrahlen, *Verhandl d Kong f inn Med* **23** 463, 1906

4 Groedel, F M. Die Roentgenbehandlung des Asthma bronchiale in Roentgenbehandlung Innerer Krankheiten, Munchen, J F Lehman, 1922

5 Pohlmann, C. Milzbestrahlung bei Bronchialasthma, Munchen med Wchnschr **72** 57 (Jan) 1925

6 Gallino, M M., and Terrada, H M. Radio-Therapy of Asthma, *Rev Soc de med Torino* **1** 132, 1925

7 Moner, G. La Radioterapia en le Esma Bronchial, *Rev Soc Argentin de Rad y Electr* **1** 19, 1925

8 Gerber, I. Roentgen-Ray Treatment in Bronchial Asthma and Chronic Bronchitis, *J A M A* **85** 1026 (Oct 3) 1925, Further Observations on the Roentgen-Ray Treatment of Bronchial Asthma and Allied Conditions, *Radiology* **9** 192 (Sept) 1927

9 Klewitz, D F. Roentgenbestrahlung bei Asthma bronchiale, Munchen med Wchnschr **69** 305 (March) 1922

Cole and Ramirez,¹⁰ who applied roentgen-ray treatment over the spleen and chest, do not, in their report, share the favorable impression of the aforementioned authors. An analysis of their records, however, indicates that the treatment of the spleen alone gave better results than the combined method. I¹¹ have previously given a detailed report of a case with the results of roentgen-ray treatment of the spleen, and I have subsequently published data obtained in ten cases.¹² The observations of the various authors¹³ are recorded in table 1. Of 171 patients, 70.1 per cent were improved, 11.7 per cent failed to respond to the treatment, and the rest did not return for observation. In the reports of these cases, however, the clinical data are either lacking or incomplete, with the exception of the ones presented by Cole and Ramirez and those reported by me. Gasul¹⁴ who applied diathermy to the spleen, reports "excellent results."

TABLE 1—*Results of Observations of Various Authors*

| | | | Total Number of Patients | Results | | | Not Returned |
|---------------------|------|------------------|--------------------------------|----------|------|------|-----------------|
| | | | | Splendid | Good | None | |
| Groedel | 1922 | Spleen | 41 | 18 | 12 | 8 | 2 |
| Pohlmann | 1925 | Spleen | 42 | | 40 | 2 | |
| Ramirez and Cole | 1925 | Spleen | 8 | | 4 | 4 | |
| Waldbott | 1925 | Spleen | 10 | | 6 | 2 | 2 |
| Gallino and Terrada | 1925 | Spleen | 26 | 12 | 10 | 2 | 2 |
| Moner | 1925 | Spleen and lungs | 22 | 7 | | 1 | 5 |
| Mueller | 1926 | Spleen and lungs | 22 | | 11 | 1 | 4 |
| | | | 171 | 120 | | 20 | 15 |

In spite of these encouraging reports in the literature, roentgen-ray treatment of patients with asthma has not been universally adopted, a fact easily explained by the following: (1) the difficulty of gaining an unprejudiced view of the efficacy of any one remedy for asthma, (2) the insufficiency of experimental evidence on the use of this treatment and (3) the insufficient knowledge of a possible injurious action of the rays on the body.

10 Cole, L. G. and Ramirez, M. A. Roentgen-Ray Therapy in Bronchial Asthma. *Am J Roentgenol* **14** 322 (Oct) 1925.

11 Waldbott, G. L. Roentgen-Ray Treatment of the Spleen in Asthma. *Arch Int Med* **36** 743 (Nov) 1925.

12 Waldbott, G. L. Treatment for Asthma and the Related Anaphylactic Diseases. *J Michigan M Soc* **24** 588, 1925.

13 Mueller, A. Roentgen-Ray Treatment of Bronchial Asthma. *Med Klin* **21** 1493 (Oct) 1925.

14 Gasul, R. Method of Treatment of Bronchial Asthma by Diathermy of Spleen. *Strahlentherapie* **21** 685, 1926.

"CURE" OF PATIENTS WITH ASTHMA

In reference to the first point Kahn¹⁵ has recently demonstrated that it is almost impossible to form an impartial opinion regarding the 'cure' of asthma. The confusion encountered in analyzing the value of a therapeutic measure is explained by the large variety of factors which contribute both to the outbreak of an attack and to its subsidence. An apparent cure may be simply a result of the temporary absence of the exciting agents. Spontaneous remissions are often of long duration and are sometimes permanent.

EXPERIMENTAL EVIDENCE

In regard to the part which the spleen plays in the causation of anaphylaxis and allergy, reference has been made in a former publication¹¹ to experiments by Luckhardt, Becht, Carrel and Ingebrigsten, Hektoen and Motohashi. These authors showed that the spleen is involved in the production of specific antibodies. Their work suggests that the removal of the spleen reduces the power of the animal to produce antibodies, whereas irradiation of the spleen increases the antibody titer of the blood. Doerr¹⁶ and Schneider¹⁷ have recently confirmed the theory that if roentgen-ray treatment is applied in proper doses, it prevents the production of anaphylaxis in animals. Although the anaphylactic experiment is not generally considered analogous to the mechanism of allergy (Coca¹⁸), the evidence obtained by these experiments suggests a close relationship of the spleen to the allergic phenomenon. Mayr and Moncorps¹⁹ observed a marked reduction in the number of eosinophils in sensitized animals following the injection of extract from the spleen. When this procedure was used on human beings who showed allergic manifestations of the skin, the same result was encountered. Should these observations be confirmed, there would be reason to believe that hypofunction of the spleen results in hyper-eosinophilia and hyperfunction of the spleen in hypoeosinophilia or aneosinophilia. In view of the almost invariable association of eosinophilia with the phenomenon of allergy, these experiments suggest that the spleen is in some way concerned in the mechanism of asthma.

15 Kahn, M. H. Present Status of Curability of Bronchial Asthma, *Arch Int Med* **39** 621 (May) 1927.

16 Doerr, quoted by Schneider. *Klin Wchnschr* **6** 1037 (May) 1917.

17 Schneider, E. Anaphylaxie und Roentgenstrahlen, *Klin Wchnschr* **6** 1037 (May) 1927.

18 Coca, A. F. *Essentials of Immunology*, Baltimore, Williams & Wilkins Company, 1926.

19 Mayr, J. K., and Moncorps, C. Eosinophilia and the Spleen, *Munchen med Wchnschr* **73** 1777 (Oct) 1926, *Studien zur Eosinophilie*, Virchows *Arch f path Anat* **264** 774, 1927.

TABLE 2—*Allergic Asthma in Children **

| No | Name | Age | Allergic History | Duration | Frequency of Attacks | Skin Sensitive to | Percent Age of Eosino- philia | Additional Observa- tions | Exposures First Last | Number of Treat- ments | Observed For | Result | Comment |
|----|------|-----|--|----------|----------------------|--|--|---------------------------------|-------------------------|---------------------------------|-----------------|--------|--|
| 1 | Fle | 1 | Eczema when 3 mo old, urticaria | 1 | 1 to 2 a week | Egg, rye, beans, tomatoes, oranges, Egg | 11 | Chronic tonsillitis | 1/20/25 | 1 | 5 mo | + | Bronchopneumonia 1 month later |
| 2 | Mar | 5 | Had eczema, four members of family had eczema | 1 | Every night | | 17 | Chronic tonsillitis | 7/26/25 8/4/25 | 2 | 3 mo | + | Patient not seen after 3 months |
| 3 | Sim | 6 | Negative | 2 | Every night | Almonds, barley, giant ragweed | 7 | Chronic choryza | 10/6/25 9/21/26 | 2 | 16 mo | ++ | |
| 4 | Mun | 3 | Sore generalized eczema | 1 | 1 to 2 a week | Egg, tomatoes | 7 | | 11/10/25 5/11/26 | 2 | 13 mo | ++ | Eczema not influenced, had varicella after treatment |
| 5 | Egi | 5 | Mother and uncle had asthma | 3 | 1 in 2 weeks | Egg, milk | 11 | Adenoids | 11/10/25 5/11/26 | 2 | 20 mo | + | Free from attacks 1 year, then one attack |
| 6 | Dur | 11 | Uncle had urticaria, grandmother had angioneurotic edema | 7 | 1 a month | Oysters | 3 | Carious teeth | 3/31/26 7/31/26 | 2 | 7 mo | — | |
| 7 | Gro | 7 | Aunt had eczema | 3 | Every 3 to 4 days | Milk | 9 | Tonsillitis | 9/28/26 12/21/26 | 3 | 8 mo | — | |
| 8 | Sch | 11 | Frequent urticaria | 8 | Every 3 to 4 months | Eggs | 9 | | 12/13/26 | 1 | 10 mo | + | |
| 9 | Tul | 7 | Mother had hay fever and asthma | 5 | 2 to 3 a month | Several fish and meats | 2 | Carious teeth | 5/31/27 | 1 | 4 mo | — | |
| 10 | Das | 12 | Father had asthma and hay-fever, mother had urticaria | 9 | Every 2 to 3 weeks | Halibut herring | 9 | Carious teeth | 6/14/27 7/25/27 | 3 | 4 mo | — | |
| 11 | Jon | 3 | Negative | 1 | Daily | B cod | 6 | Chronic tonsillitis | 7/24/25 8/25/25 | 1 | 6 mo | ++ | Well for 13 months, then few attacks |
| 12 | Spe | 10 | Hay fever, gastro intestinal disturbances | 7 | 2 a week | Micrococci caraboli, Streptococcus hemolyticus | 5 | Dental infection | 9/8/25 | 1 | 13 mo | + | Well for 1 year, relapse after toxoid injection |
| 13 | Ben | 9 | Urticaria 4 years ago | 1 | 1 in 2 weeks | Horse serum | 11 | | 12/2/25 1/1/26 | 2 | 16 mo | + | No improvement |
| 14 | Rou | 6 | Mother had hay fever | 2 | 1 a week | Streptococcus non hemolyticus | 14 | Chronic tonsillitis | 5/31/26 12/7/26 | 1 | 6 mo | — | |
| 15 | Bro | 1½ | Father had hay fever, uncle had asthma | 1 | 2 a month | Negative | 6 | Tonsillitis | 11/28/26 1/25/27 | 2 | 10 mo | ++ | |
| 16 | Hol | 4 | Father had eczema, frequent urticaria | 3 | Every 1 to 3 nights | Streptococcus non hemolyticus | 3 | Sinusitis | 5/13/23 5/27/26 | 1 | 17 mo | ++ | |
| 17 | Tos | 10 | Eczema during infancy | 1½ | 1 to 2 a week | Negative | 8 | Congenital syphilis | 3/22/25 12/1/25 | 2 | 2½ yr | + | Practically free from asthma now |
| 18 | Hal | 4 | Father had asthma and hay fever | 3½ | 1 to 2 a week | Negative | 6 | Tonsillitis | 3/8/27 3/20/27 | 3 | 4 mo | — | |

| | | | | | | | | | | | | |
|----|------|-------|--|----|-----------------------------|------------------------------------|------------------------|----------|----------|-------|-------|----|
| 19 | Guy | 6 | Grandfather had asthma, formerly eczema | 1 | 1 a week | Negative | Chronic tonsillitis | 11/23/26 | 1 | 12 mo | ++ | |
| 20 | Hut | 6 | Urticaria | 1 | Every night | Negative | Chronic tonsillitis | 1/25/27 | 1 | 6 mo | + | |
| 21 | Jel | 1 | Mother had hay-fever and asthma, sister had eczema | 2 | 1 a month | Negative | Chronic tonsillitis | 1/26/27 | 1 | 6 mo | ++ | |
| 22 | Shu | 8 | Mother's father and father's mother had asthma, patient had eczema | 5 | Each fall for several weeks | Giant ragweed | | 6/11/26 | 7/12/26 | 1 | 10 mo | — |
| 23 | Mels | 11 | Hay fever | 7 | Every 2 to 3 months | Giant ragweed | Chronic myocarditis | 11/23/26 | 1/ 1/27 | 2 | 5 mo | + |
| 24 | Dec | 6½ | Frequent vomiting after eating vegetables | 1 | 1 in 1 to 2 weeks | Milk, casein, wheat, egg | Cirrhosis teeth | 7/25/24 | 8/18/25 | 2 | 3 yr | + |
| 25 | Zm | 12 | Urticaria frequently | 5 | 1 every night | Cocoa, wheat, beans, chicken, pork | | 9/ 8/25 | 9/25/25 | 2 | 13 mo | ++ |
| 26 | Haz | 5 | Mother and uncle had asthma | 1 | 1 1 month | Egg | | 11/23/25 | 1/21/26 | 3 | 20 mo | — |
| 27 | Gab | 2½ | Grandmother had asthma and hay-fever, child had urticaria | 2 | 1 in 2 weeks | Egg, pneumococcus | Rhinitis | 11/ 2/26 | 11/16/26 | 2 | 12 mo | + |
| 28 | Kat | 3 | Eczema when 6 months old | ½ | Every night | Milk, staphylococci | Chronic tonsillitis | 12/ 6/26 | 1/ 2/27 | 3 | 8 mo | ++ |
| 29 | Kel | 10 | Sister had infantile eczema | 5 | Continuously for 4 months | Feathers | | 9/ 7/26 | 9/21/26 | 3 | 13 mo | ++ |
| 30 | Tai | 3 | Vasomotor rhinitis (perennial) | 1½ | Every 3 weeks | Negative | Chronic tonsillitis | 8/ 2/26 | 1/25/27 | 2 | 7 mo | ++ |
| 31 | Pet | 12 | Negative | 10 | 3 a week | Negative | Chronic tonsillitis | 9/21/26 | 9/28/26 | 2 | 1 mo | — |
| 32 | Urb | 9 | Eczema | 7 | Every 3 weeks | Negative | Slight thyroid adenoma | 6/26/27 | | 1 | 4 mo | + |
| 33 | Low | 1 | Negative | 3½ | 2 to 3 a week | Pollens and epidermis extracts | | 11/ 9/26 | 1/11/27 | 2 | 5 mo | + |
| 34 | Fal | 10 | Father had hay-fever, patient had urticaria | 7 | Every 2 weeks | Several bacteria and pollens | | 3/15/27 | 1/23/27 | 3 | 3 mo | — |
| 35 | Oha | 5 | Eczema | 2 | Every 2 to 3 nights | 1 egg, feathers | Chronic tonsillitis | 11/25/21 | 12/ 9/21 | 2 | 3 yr | + |
| 36 | Wat | 6 | Negative | 1 | Every night | Negative | Chronic tonsillitis | 8/ 4/25 | | 1 | 6 mo | — |
| 37 | Cam | 3 | Sister had eczema, grandfather had asthma | 3 | 5 to 6 a year | Negative | | 1/11/27 | | 1 | 10 mo | ++ |
| 38 | Man | 16 mo | Had urticaria, grandmother had asthma | 1 | 1 every 2 to 3 months | Negative | | 1/26/27 | | 1 | 6 mo | + |
| 39 | Cas | 6 | Grandmother and mother had asthma | ¼ | 1 to 2 a month | Negative | | 5/10/27 | | 1 | 5 mo | — |

* In the tables, + indicates that there was temporary relief, ++, symptom free and —, that the patient was not improved following treatment

TABLE 3—*Allergic Asthma in Adults*

| No | Name | Age | Allergic History | Asthma for Years | Frequency of Attacks | Skin Sensitive to | Percent Eosinophils | Associate Observations | First Treatment | Last Treatment | Number of Exposures | Observed After Treatment For | Result | Comment |
|----|------|-----|--|------------------|-----------------------|--|---------------------|------------------------|-----------------|----------------|---------------------|------------------------------|--------|---|
| 10 | Bri | 50 | Vasomotor rhinitis (perennial) | 25 | Daily | None | 0 | Empysemata | 6/ 1/25 | 8/ 5/25 | 5 | 17 mo | + | Relapse after 3 months |
| 11 | Ort | 41 | Sister had hay fever and urticaria | 10 | 2 to 3 a week | Horse dander, goose feathers, Streptococcus nonhemolyticus | 5 | | 6/10/26 | 6/22/26 | 2 | 12 mo | ++ | |
| 12 | Bah | 23 | Hay fever at age of 7 years | 1 | Very 2 to 3 nights | lyticus | 10 | Septum de flection | 8/17/26 | 8/24/26 | 2 | 14 mo | + | Had two slight attacks only |
| 13 | Tho | 40 | Hay fever until 10 years ago, uncle had asthma | 15 | Every night | Streptococcus non hemolyticus, Staphylococcus aureus | 14 | One devitalized tooth | 11/11/25 | 12/15/25 | 1 | 10 mo | ++ | |
| 14 | Sin | 67 | Sister had asthma | 10 | 1 every second night | Negative | 3 | Septum devitalized | 3/ 9/26 | 4/10/26 | 2 | 3 mo | + | Free from attacks for 3 months |
| 15 | Ioh | 52 | Brothers and sisters had eczema and urticaria | 23 | 1 to 2 attacks a week | Herring | 3 | Urticary syphilis | 1/18/27 | 2/18/27 | 2 | 8 mo | + | |
| 16 | Kno | 49 | Eczema for 9 years, hay fever | 19 | Continuously | Strawberry, egg, B. coli, Staphylococcus aureus | 8 | | 7/13/25 | 8/25/25 | 3 | 19 mo | — | Well since fall of 1926 without other therapy |
| 17 | Pla | 39 | Brother had urticaria, mother had asthma | 1 | Every night | Staphylococcus aureus, nuts, celery | 2 | | 5/23/27 | 6/ 1/27 | 2 | 6 mo | — | |
| 18 | Win | 32 | Mother and cousin had asthma, child had eczema | 6 | Daily | Almonds | 1 | Nasal polypl | 4/12/27 | 6/ 7/27 | 1 | 5 mo | — | Improved for 3 weeks, but subsequent relapse |
| 19 | Tho | 33 | Two sisters of grandfather had asthma | 1½ | Days and nights | Acetylsalicylic acid | 10 | Thinolditis | 6/ 6/25 | 8/ 7/25 | 3 | 1½ yr | + | Relieved 3 months, then as before |
| 20 | Mar | 33 | Father and brother had asthma, baby had eczema | 1 | Daily | Mints and fish, tobacco | 10 | Glycoid adenoma | 10/18/26 | 10/20/26 | 2 | 8 mo | — | |
| 51 | Gan | 29 | Mother and brother had asthma, sister had eczema | 8 | 2 to 3 a week | Negative | 3 | Nasal polypl | 3/15/26 | 4/12/26 | 2 | 19 mo | ++ | |

In the following studies in order to gain further insight into the influence of the spleen on allergic conditions, I have used roentgen-ray treatment over the spleen only. Irradiation of the chest was purposely omitted.

METHOD

In the cases recorded, the patients were under continuous observation during a period of from three months to three years. During this time, other treatment was not administered, with the exception of emergency measures during acute attacks. The patients were advised not to eliminate contact with known exciting substances. Patients with asthma who were sensitive to food were asked particularly not to exclude from their diet food to which they were sensitive.

The roentgen-ray treatment was administered by the roentgen-ray departments of the clinics. In the technic, the directions of Groedel were followed, 5 milliamperes, 4 mm of aluminum, 88 kilowatts at 10 inch skin target distance were applied for six minutes. As a rule, two treatments were administered at intervals of two weeks. The number of treatments and intervals between treatments were, however, adjusted to the individual case (column 11 in tables 2, 3 and 4).

Before the treatment was instituted, the patients were carefully studied in an attempt to gain as much insight into the individual condition as possible. Skin tests, eosinophil counts and radiographs of the chest were made as routine procedures. In questionable cases, epinephrine was administered as a therapeutic test. Determinations of the blood calcium (Brown,²⁰ Wilmer²¹) were made for a number of patients, but later this was abandoned because the results were too inconstant to be of value in distinguishing allergic asthma from other asthma-like conditions. On the basis of these studies, the patients were grouped according to the etiology found (table 5).

In tables 2 and 3 are given the data for patients in whom the condition was definitely diagnosed as allergic asthma, in table 2 those of patients who were less than 15 years of age, and in table 3 those of patients 15 years of age or more. Following the procedure of Rackemann,²² these patients were grouped according to their sensitiveness to bacteria, food, pollen and emanation. It should be noted, however, that this classification is not entirely satisfactory, because many asthmatic patients are sensitive simultaneously to several substances (Peshkin²³). In table 4 are recorded the cases of hay-fever, angioneurotic edema, urticaria and eczema. Since these conditions are etiologically closely related to asthma it was hoped to secure a broader view of the value of roentgen-ray therapy of the spleen by submitting these patients to this treatment. Table 4 also includes the data of cases in which the patients manifested

20 Brown, G. T. Calcium Deficiency in Asthma, Hayfever and Allied Conditions, *Ann Clin Med* **4** 299, 1925.

21 Wilmer, H. B. Treatment of Bronchial Asthma, *J A M A* **89** 956 (Sept 17) 1927.

22 Rackemann, R. M. Clinical Classification of Asthma Based upon a Series of 648 Cases, *Am J M Sc* **162** 802 (Dec) 1921.

23 Peshkin, M. M. Asthma in Children, *Am J Dis Child* **31** 763 (June) 1926.

TABLE 4—Associated Conditions

| No | Name | Age | Allergic History | Dura- tion | Frequency of Attacks | Skin Sensitive to | Percent age of Eosino- philia | Additional Observa- tions | First Expo- sure | Last Expo- sure | Number Observed of Treat- ments | For | Treatment Result | Comment |
|---|------|-----|--|---------------|------------------------------|--|--|---------------------------------|------------------------|-----------------------|--|-------|---------------------|--|
| 52 | Ami | 6 | Frequent vomiting after eating vegetables | 1 yr | 1 to 2 a week | Cabbage, earrot, veal, chicken | 9 | Pyorrhea, eruptive teeth | 11/12/24 | 2/24/25 | 4 | 3 yr | ++ | Had ehorena during observation |
| 53 | Kes | 9 | Negative | 6 mo | Every morn- ing | Negative | 2 | Negative | 12/15/24 | 12/30/24 | 2 | 1 yr | ++ | |
| 54 | Cau | 4 | Eczema as baby, grandmother had asthma | 2½ yr | 2 to 3 a week | Micrococci catar- rhals, Streptococcus pyogenes, wheat Oranges, tomatoes, prunes | 0 | Infected teeth | 9/21/26 | 9/28/26 | 2 | 5 mo | + | |
| 55 | Sto | 13 | Perennial rhinitis, eczema, mother had hay fever | 6 mo | Daily wheezing | | 12 | Chronic tonsillitis | 11/ 2/26 | 12/31/26 | 4 | 8 mo | ++ | |
| 56 | Bre | 13 | Eczema | 1 yr | Every night | Negative | 3 | Negative | 4/10/27 | | 1 | 6 mo | ++ | |
| Tuberculosis and Asthma | | | | | | | | | | | | | | |
| 57 | Eck | 9 | Cousin had asthma | 2½ yr | Every second or third day | Negative | 5 | Formerly tuberculosis | 2/17/25 | 11/24/25 | 3 | 2 yr | — | Relief following tu- berculin treatment |
| 58 | Nov | 6 | Negative | 1 yr | 3 attacks in 6 months | Pirquet | 10 | Beginning tuberculosis | 8/11/25 | 11/24/25 | 3 | 9 mo | — | Well for 10 months, died following pneumonia |
| 59 | Bor | 42 | Urticaria, hay fever | 8 yr | Constantly in winter | Negative | 1 | Tuberculosis | 1/10/26 | 2/ 7/26 | 2 | 10 mo | — | |
| 60 | En | 72 | Negative | 1 yr | Every night | Negative | 2 | Tuberculosis | 6/10/26 | | 1 | 9 mo | — | |
| Chronic Nonspecific Bronchitis Following Asthma | | | | | | | | | | | | | | |
| 61 | Bal | 62 | Had hay fever | 25 yr | Every second or third day | Ragweed | 10 | Chronic myocarditis | 11/27/25 | | 1 | 10 mo | — | |
| 62 | I ev | 57 | Had hay fever | 11 yr | Every night | Negative | 1 | Myallir sinusitis | 9/24/26 | 12/ 6/26 | 2 | 1 yr | — | |
| 63 | Har | 67 | Had hay fever and frequent urticaria | 12 yr | Every 3 or 4 days | Beans and fish | 1 | Chronic myocarditis | 5/ 2/27 | 5/12/27 | 2 | 3 mo | — | |
| Bronchiectasis Following Asthma | | | | | | | | | | | | | | |
| 64 | Sut | 37 | Negative | 35 yr | 2 to 3 a week | Tomatoes | 2 | Bronchi- ectasis | 9/21/25 | 10/19/25 | 2 | 16 mo | — | Relieved for 2 mo |

[illegible]

the asthmatic symptom complex of wheezing and dyspnea, the cause of which was determined to be other than allergic, namely hypertrophy of the thymus. The cases of four patients with asthma on the basis of tuberculosis are also reported. The treatment was given to the two patients with hay-fever as prophylaxis before the expected onset of symptoms. Several patients with hay-fever received the roentgen-ray therapy during the season, but the results are not recorded because the treatment was administered too close to the expected time of the subsidence of symptoms to permit fair judgment of its value. In interpreting the results, I have relied on the patient's personal statement in conjunction with my own observation and the opinion of the referring

TABLE 5—*Etiologic Classification of Cases*

| Types | ++ | + | — | Total |
|---|----|----|----|-------|
| Allergic Asthma (tables 2 and 3) | | | | |
| Food | 2 | 4 | 4 | 10 |
| Pollen | — | 1 | 1 | 2 |
| Bacteria | 7 | 8 | 2 | 17 |
| Emanation | 2 | 1 | 2 | 5 |
| Food and pollen | 1 | 1 | — | 2 |
| Food and bacteria | 1 | 1 | 3 | 5 |
| Food and emanation | — | 1 | 1 | 2 |
| Pollen and emanation | — | 1 | — | 1 |
| Bacteria and pollen | — | — | 1 | 1 |
| Unknown causes | 2 | 2 | 2 | 6 |
| | 15 | 20 | 16 | 51 |
| Associated Conditions (table 4) | | | | |
| Allergic bronchitis | 4 | 1 | — | 5 |
| Tuberculosis and asthma | — | — | 4 | 4 |
| Chronic nonspecific bronchitis following asthma | — | — | 3 | 3 |
| Bronchiectasis following asthma | — | — | 1 | 1 |
| Hay fever and asthma (prophylactic treatment) | — | 2 | — | 2 |
| Vasomotor rhinitis | 1 | — | 2 | 3 |
| Urticaria | 1 | — | 2 | 3 |
| Angioneurotic edema | — | 2 | — | 2 |
| Infantile eczema | — | — | 4 | 4 |
| Thymus hypertrophy | — | — | 3 | 3 |
| | 6 | 5 | 19 | 30 |

physician. The designation "symptom-free" (xx) is applied only to cases in which the patient has been under observation for at least six months following the treatment. The term "temporary relief" (x) indicates that the asthmatic attacks were markedly reduced in frequency as well as in severity for a limited lapse of time. This group includes some patients who were "symptom-free" when last seen, but who did not return for observation for a sufficiently long period of time to be classified in this group. The patients not relieved (—) were the ones who did not show improvement within three weeks after the last exposure. Other therapeutic measures were administered to these patients later, and a considerable number were improved, but their relief from symptoms was not attributed to the roentgen-ray therapy. As a whole, an attempt was made to be conservative in interpreting the results. The designation "cured" has purposely not been used, because one should be

aware of the fact that even though a patient is symptom-free for several years, an attack is apt to occur at some future time

RESULTS

In a total of eight-one cases, twenty-one patients were symptom-free, twenty-five were temporarily relieved and thirty-five, of 43.2 per cent, did not respond to the treatment. Of fifty-one patients with allergic asthma (tables 2 and 3), fifteen remained symptom-free, twenty were temporarily relieved, and sixteen did not respond to the treatment, representing 31.3 per cent of failures.

In table 2 the records of thirty-nine children show 30.8 per cent of failures, in table 3, presenting twelve adults, the figures show 33.3 per cent of failures. Table 4 shows the results of treatment of patients suffering from asthma complicated by other conditions and also patients with other allergic diseases, only six of thirty patients

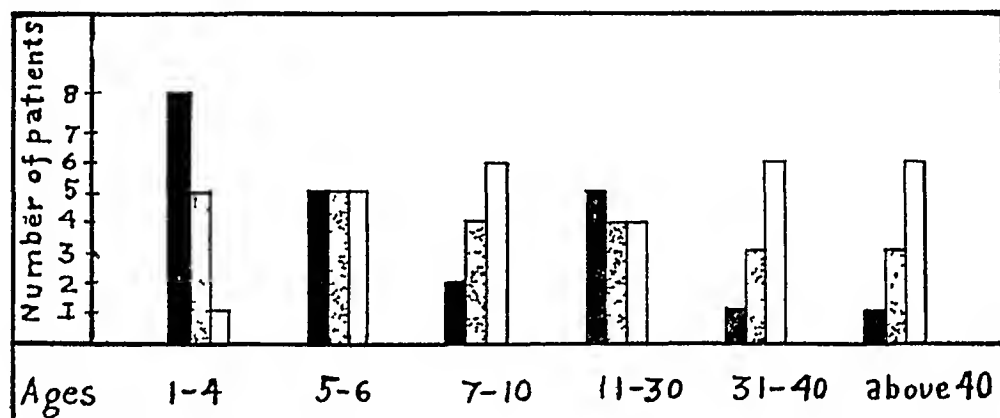


Fig 1—Efficacy of treatment in patients of various ages. The black columns indicate that the patients were symptom free, the dotted columns that there was temporary relief and the blank columns that the patients were not improved.

were symptom-free, five were temporarily relieved, and nineteen, or 63.3 per cent, did not respond. The details are given in table 5, which reveals that patients who had asthma complicated by tuberculosis or chronic bronchitis (emphysema) did not show improvement. Likewise, patients with eczema and "asthma" due to hypertrophy of the thymus did not benefit by the treatment. The results in cases of hay-fever, urticaria and vasomotor rhinitis are uncertain. In patients with allergic bronchitis, the treatment was most effective. Allergic bronchitis is a condition characterized by cough and expectoration due to allergy, but it is not sufficiently severe to produce attacks (Duke²⁴). The results in table 5 also indicate that in bacterial cases the patients were relieved

²⁴ Duke, W. W. Allergy, Asthma, Hay-Fever and Allied Manifestations, St. Louis, C. V. Mosby Company, 1926.

by this treatment more generally than in other cases. The age of the patient furnished information that was of some prognostic value. An analysis of figure 1, in which the age of the patients is compared with the efficacy of the treatment indicates that the greatest number of improvements occurred in the younger and the greatest number of failures in the older patients.

REACTION

Most observers noticed a marked "reaction" after the treatment, consisting mainly of nausea, vomiting, headache, dizziness and, occa-

TABLE 6—*Observation on Reactions*

| Case | Exposure on | Reaction* | Days Following Treatment | Result |
|------|-------------|-----------|--------------------------|--------|
| 2 | 7/26/25 | V N | 5 | + |
| | 8/ 4/25 | D | 2 | |
| 3 | 9/21/26 | P | 2 | ++ |
| 4 | 10/13/25 | V | 1 | ++ |
| 5 | 11/10/25 | V N | 2 | + |
| | 5/11/23 | P V | 2 | |
| 6 | 3/31/26 | V | 1 | — |
| 7 | 12/21/26 | V P | 4 | — |
| 8 | 12/13/26 | P | 2 | — |
| 12 | 9/ 8/25 | V P A | 2 | + |
| 13 | 12/ 2/25 | D V P A | 2 | + |
| 14 | 5/21/26 | D | 1 | — |
| 17 | 3/22/25 | N A | 4 | + |
| 21 | 4/26/27 | N | 1 | ++ |
| 24 | 11/23/26 | D V | 5 | ++ |
| 25 | 9/ 8/25 | N D | 2 | ++ |
| 26 | 11/23/25 | V N | 1 | — |
| 28 | 1/ 5/27 | V A | 2 | ++ |
| 32 | 6/26/27 | A | 1 | + |
| 34 | 4/23/27 | N D | 2 | — |
| 42 | 8/24/26 | N V P | 2 5 | + |
| 48 | 4/12/27 | V N D | 1 | + |
| 49 | 7/21/25 | P N | 3 | + |
| 51 | 3/15/26 | V N | 1 | ++ |
| 52 | 11/12/24 | A | 5 | ++ |
| 53 | 12/15/24 | V | 2 | ++ |
| 55 | 11/ 2/26 | V N | 2 | ++ |
| | 11/19/26 | D P | 2 | |
| 59 | 11/23/27 | V | 1 | — |
| 60 | 11/30/23 | N V P | 3 | — |
| 62 | 1/10/23 | V | 2 | — |
| 63 | 6/10/26 | N | 2 | + |
| 65 | 9/24/26 | P N V | 1 | ++ |
| 68 | 8/ 7/26 | N | 2 | + |
| 72 | 5/28/27 | N V | 2 | — |
| | 7/ 8/27 | N | 2 | |
| 79 | 12/ 8/25 | V | 2 | + |

* N indicates nausea, V, vomiting, P, abdominal pain, and A, asthmatic attack

sionally, a severe attack of asthma. Groedel expressed the opinion that this reaction may possibly be an obligatory factor to a subsequent cure, and he felt that the severity of the reaction was in direct proportion to the degree of relief obtained. Gerber believed that the occurrence of the reaction is due to the administration of too large doses of the roentgen ray. On restricting the exposures to the mediastinum only, he observed less severe reactions. Observations in regard to this question are recorded in table 6. One hundred and sixty-nine treatments were administered to eight-one patients. Of this number, only thirty-seven treatments given to thirty-three patients were followed by reactions.

Ten of these patients were symptom-free, thirteen were temporarily relieved and ten did not improve. There were, therefore, only 30 per cent of failures among these cases as compared with 43.2 per cent of the whole total. Thus, on the whole, the occurrence of a reaction was accompanied by better results. The severity of the reaction in the individual case however did not determine the degree of relief, as a close analysis of table 6 reveals. The reaction usually occurred on the second day, nausea and vomiting were the predominating symptoms. In five cases a severe attack of asthma followed the treatment, in one, a marked urticaria. In one patient who was treated after the conclusion of these studies, extensive eczema developed on the site of exposure, whereas the asthma disappeared completely.

LUNGS

Groedel, Gerber, Mueller and others noticed a marked increase in expectoration among the patients who improved. I did not always observe this phenomenon. Some patients developed a severe, dry,

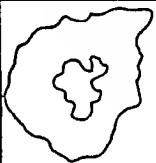


| 7-19-27 | 7-29-27 | 8-2-27 | 8-5-27 | 8-9-27 | 8-16-27 |
|--|--|--|----------|----------|----------|
|  |  |  | negative | negative | negative |

Fig 2 (case Skok) —Variation of skin reaction (egg) following irradiation of the spleen. Treatment was given on July 26, 1927.

unproductive cough which lasted from one to two weeks, apparently taking the place of the asthmatic attacks. In patients 29 and 51, in whom this peculiar bronchitis was seen, the subsequent relief from asthma was extremely spectacular. On reexamination of the chest by the roentgen ray after the treatment however definite changes in the appearance of the glands of the hilum were not detected. The patients designated as "symptom free" were entirely free from the physical signs of asthma on frequent reexamination of the lungs. In a few cases, hyper-resonance of the percussion note was the only sign encountered.

SKIN TESTS

In all previous reports on roentgen-ray treatment for asthma, reference to skin tests has not been made. In this study, as a rule, parallelism was not observed between the diminution in the size of the area sensitized and the improvement of the patient. In some instances however, the positive reaction of the patient became negative as he improved. This change occurred within the first five or six days following the

treatment (fig 2 and table 7) A change in the size of the sensitized area was not found within the first twenty-four hours In some patients, the reaction to the skin tests remained negative for months On

TABLE 7—Record of Percutaneous Skin Tests in Case 1 Before and After Treatment Which Was Given on Jan 20, 1925

| January 16 | | January 21—One Day After Treatment | | January 26—Six Days After Treatment | |
|--------------|-----|---------------------------------------|----|--|---|
| Beef | — | Beef | — | Beef | — |
| Chicken | — | Chicken | — | Chicken | — |
| Milk | — | Milk | — | Milk | — |
| Eggs | +++ | Egg | ++ | Egg | — |
| Rye | + | Rye | — | Rye | — |
| Oats | — | Oats | — | Oats | — |
| Corn | — | Corn | — | Corn | — |
| Beans | + | Beans | — | Beans | — |
| Spinach | — | Spinach | — | Spinach | — |
| Tomatoes | + | Tomatoes | — | Tomatoes | — |
| Strawberries | — | Strawberries | — | Strawberries | — |

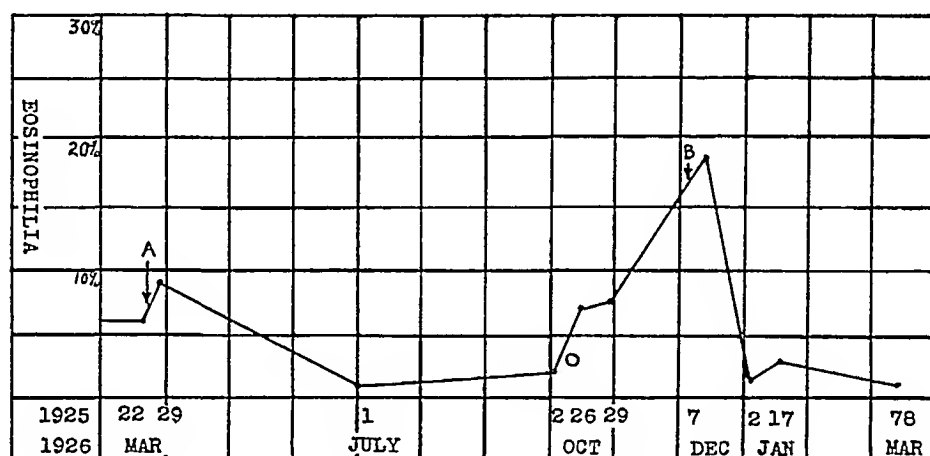


Fig 3 (case 17)—Effect of irradiation of the spleen on eosinophilia A indicates the first and B the second roentgen-ray treatment The patient had one or two attacks per week preceding treatment The dotted circle indicates the occurrence of the only attack during the period of treatment

the other hand, a patient (23) in whom a 3 plus ragweed test never became negative was freed from asthma and hay-fever

EOSINOPHILIA

Previous observers (Pohlman, Mueller and others) report a decrease in the number of eosinophil cells following the treatment In the majority of cases I had the same experience, with the exception, however, that within the first one or two days, hypereosinophilia was noted (fig 3) When the blood was examined within the first two or three hours, I found an increase in eosinophilia already present The eosinophilia reached its highest degree at the time of reaction, and it

usually decreased below its original level within the first two or three weeks following. In patients in whom a high eosinophilia was present, a further increase did not take place. This is exemplified by case 29 (fig 4). A relationship did not exist between the degree of eosinophilia before the treatment and the degree of improvement obtained (table 8).

TABLE 8—*Relationship of Efficacy of the Roentgen-Ray Treatment Over the Spleen to Eosinophil Count Previous to Treatment*

| Number of Cases with Eosinophilia of | Result | | | Total | Percentage of Failures |
|---|--------|----|----|-------|---------------------------|
| | ++ | + | — | | |
| 0 to 5 per cent | 8 | 14 | 14 | 36 | 39.7 |
| 6 to 10 per cent | 7 | 6 | 13 | 26 | 50 |
| 11 to 15 per cent | 3 | 5 | 2 | 10 | 20 |
| Above 15 per cent | — | 1 | — | 1 | — |
| | 18 | 26 | 29 | 73 | |

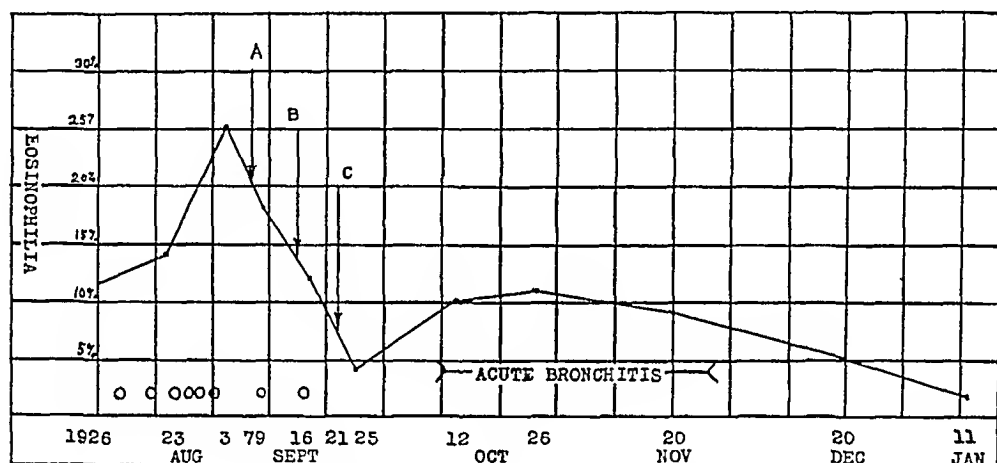


Fig 4 (case 29)—Effect of irradiation of the spleen on eosinophilia. *A* indicates the first exposure, *B*, the second, and *C* the third. The dotted circles indicate the occurrence of attacks of asthma. The patient did not have any attacks following the third exposure.

COMMENT

The explanation of these results is difficult, since the knowledge both of the relationship of the spleen to allergy and of the etiology of asthma itself is too vague to make any definite conclusion possible. Many theories are offered by the various authors. Groedel speculates on the possibility of stimulating the function of the spleen by the roentgen ray. He thinks that certain substances might thus be activated to counteract the allergic state. On the basis of this theory, Gasul employs diathermic treatment of the spleen as a means of stimulating this organ. Gerber assumes that destruction of tissue of the spleen rather than its stimulation might be the effect of roentgen-ray therapy. He holds that the

foreign protein created by the destroyed tissue of the spleen is responsible for the relief obtained. Such a theory is plausible in view of the great improvement achieved in the treatment of patients with asthma by the parenteral use of various foreign protein agents, such as tuberculin (van Leeuwen and Varekamp²⁵), vaccine (Brown²⁶), peptone injections (Pasteur Vallery-Radot²⁷) and many others.

In a previous publication,¹¹ I showed that the reticulo-endothelial system as well as the lymphatic apparatus might be involved in the process of production of antibodies. In both of these systems, the spleen plays an important rôle. In spite of the extensive research to determine the function of the spleen, the question of the relationship of these two systems to allergy has not as yet been sufficiently considered. The outcome of the foregoing studies warrants further investigation in this matter.

The question arises as to how much of the improvement observed in these patients is due to psychic influence (Nietzsche, Levy-Dorn²⁸). Since the classical work of Walker,²⁹ the old theory of "asthma nervosum" has been abandoned. Recent contributions to literature (Ziegler and Elliott³⁰), however, make it probable that the mental status of a person has at least some bearing on the elicitation and termination of asthmatic attacks. I attempted to give my patients as little encouragement concerning the efficacy of the treatment as possible. Most of the children were submitted to the treatment with the idea that it was "just another test," and they returned relieved without realizing that a treatment had been administered. Several children were less than 2 years of age, among these the possibility of a psychic "cure" can be definitely ruled out.

In applying a measure such as roentgen-ray treatment over the abdomen, one should be aware of the fact that there are several objections, at least theoretically, to such a treatment for a benign disease. One might speculate on the possibility of exciting a latent cancerous growth in the irradiated area. Moreover a destruction of the tissue of the spleen might cause a permanent change in the blood picture or might

25 Van Leeuwen, W. S., and Varekamp, H. Tuberculin Treatment of Bronchial Asthma and Hay-Fever, *Lancet* **12** 1366 (Dec.) 1921.

26 Brown, G. T., and Hunter, A. Bacterial Vaccines in Asthma, *Am J M Sc* **171** 156 (Jan.) 1926.

27 Pasteur Vallery-Radot and Blamontier. Intradermal Injections of Peptone in Treatment of Anaphylactic Diseases, *Bull et mem Soc med d hôp de Paris* **51** 491 (May) 1927.

28 Nietzsche, Levi-Dorn, quoted by Groedel (footnote 4).

29 Walker, I. C. Studies on Sensitization on Patients with Bronchial Asthma, *J M Research* **35** 487, 497, 509, 1917.

30 Ziegler, L. H., and Elliott, D. C. The Effect of Emotion on Certain Cases of Asthma, *Am J M Sc* **172** 860 (Dec.) 1926.

lower the resistance of the patient against intercurrent infections. Careful search has been made for any such occurrence. Although irradiation of the spleen has been widely employed on the continent since 1921, when Stephan³¹ advocated its application for controlling hemorrhage, adverse sequelae have not been reported in the literature. Harbinson³² failed to find any pathologic changes in the blood picture in postmortem and clinical studies on rabbits that had received doses of roentgen ray many times larger than those administered to human beings. Furthermore, it has been said that the spleen may be removed from the human body without ill effect.

Frequent examinations of the blood were made in some of the patients for three years following the treatment, and indications of pathologic changes in the blood were not discovered. There were, however, two occurrences which should not be omitted from this report. In case 25, the patient remained entirely free from asthma for one year but nephrosis developed thirteen months after the treatment which resulted in death. In case 59, the asthmatic condition was improved for ten months, but the patient succumbed to fulminating pneumonia which appeared to be tuberculous in origin. The death of these children cannot be attributed to the treatment, the allergic disease itself might have impaired the resistance of these patients to infection, or, what is more probable, the intercurrent events did not bear any relationship to the original condition. On account of this experience, however, one should use discretion in applying this treatment.

SUMMARY

1 Eighty-one patients with asthma and associated allergic conditions were treated with small doses of roentgen ray over the spleen. Eighteen of fifty-six children became symptom-free, sixteen were temporarily relieved, and twenty-two did not respond to the treatment. Three of twenty-five adults became symptom-free, nine were temporarily relieved, and thirteen were not improved. In other words, there were 39.4 per cent failures among the children and 52 per cent among the adults. The patients designated as "symptom-free" were under observation for a period of time varying between six months and more than three years.

2 Patients less than 4 years of age showed the best results, and the treatment in patients more than 30 years of age was less effective. Patients afflicted simultaneously with tuberculosis and the chronic emphysematous type of asthma did not respond to the treatment. In cases of infantile eczema and an hypertrophying thymus the condition

31 Stephan, R. Blutung und Blutstillung. *Munchen med Wchnschr* **68** 746 (June) 1921.

32 Harbinson, C. H. The Effect of Roentgen-Ray Energy on the Spleen. *J. M. Research* **67** 529, 1924.

did not improve. The best results were seen among the patients with a beginning allergic condition manifested by allergic bronchitis. Better results were obtained among patients with asthma who were sensitive to bacteria than among those sensitive to food, pollen and emanation.

3 In some patients who improved, the positive skin tests became negative within the first week after the treatment.

4 As a rule, the number of eosinophils increased immediately after the treatment and returned to normal subsequently. A relationship did not exist between the degree of eosinophilia preceding the treatment and the efficacy of the irradiation of the spleen.

5 Thirty-seven of a total of 169 exposures were followed by reactions characterized by vomiting, nausea, abdominal pain or an asthmatic attack from one to five days after the treatment. Better results were encountered among these patients.

6 The value of the treatment is discussed, and warning is given against its indiscriminate use. The opinion is expressed that it should be applied only in cases of allergy in which the patients do not respond to the ordinary methods.

After the completion of the foregoing studies, the patients in the following additional cases reported at the clinic following the roentgen-ray treatment.

REPORT OF ADDITIONAL CASES

CASE 82—Skok, a boy, aged 4, gave a history of having had attacks of asthma for the past two years, which were promptly brought on by ingestion of eggs. They were usually associated with vomiting and dry cough and responded to treatment with epinephrine. Two brothers had eczema, otherwise the family history was negative regarding allergy. The patient had previously attended the clinic for patients with heart diseases, where a diagnosis of congenital pulmonary stenosis was made. Aside from these observations, the physical examination revealed poor expansion of the lungs, a few asthmatic bruits and silent hyperresonance. Skin tests with a large number of extracts were negative, with the exception of a 3 plus reaction to the skin test for eggs.

The patient was given one roentgen-ray treatment over the spleen on July 26, 1927. Several hours subsequent to the treatment, he had had a slight attack of vomiting. The appearance of the skin reaction is given in figure 4. He developed a dry, convulsive cough on August 2, which lasted until Aug 26, 1927. With the exception of a slight attack of wheezing on November 25, which his mother attributed to an infection of the upper respiratory tract, he has been free from attacks and has been able to eat eggs without discomfort.

He was last seen on Feb 3, 1928, when the skin test for egg was negative.

CASE 83—Beb, a boy, aged 3, presented a history of having had severe asthmatic attacks for the past two years. They were often preceded by colds and were inevitably elicited by eating apples. The mother's cousin and great grandmother had had asthma. True asthmatic attacks were demonstrated on several occasions when the child ate apples in the clinic. The physical examination made during an attack revealed the typical signs of asthma, the attacks were relieved by treatment with epinephrine. A series of intradermal skin tests

revealed reaction with apples, 2 plus, and *Staphylococcus aureus*, 1 plus. There was an eosinophilia of 5 per cent.

The roentgenogram of the chest revealed some hypertrophy of the hilar glands. There was no evidence of tuberculosis, thymus hypertrophy and bronchiectasis.

The child was given two roentgen-ray treatments on Nov 1, 1926, and on December 7. On December 9, the blood count showed 16 per cent eosinophils. At this time, the child was slightly dyspneic. He has never had another attack since. On May 3, 1927, the eosinophil count was 1 per cent, the skin tests were negative and the child could eat apples without distress. Owing to the fact that he suffered from a cough which appeared to be an allergic bronchitis, however, the patient was given another treatment on May 24, 1927. This treatment did not elicit a reaction.

On Feb 24, 1928, the mother said that the boy had never had another attack of asthma. He rarely has colds now. The results of physical examination were negative.

CASE 84—La Fr, a boy, aged 3½ years, had had bronchial asthma for two years. The attacks occurred every third or fourth week. Several members of the mother's family had suffered from asthma, hay-fever and eczema. During the first year of his life, he had frequent convulsions, which the mother attributed to the ingestion of eggs. She also said that the odor of mustard nauseated him and that once, after a mustard plaster was put on his chest, he had a severe seizure of urticaria. When first examined on Sept 23, 1927, there was a papulous exanthem distributed over the buttocks. The skin tests revealed sensitiveness to eggs, cheese, peas, mustard, black pepper, timothy and Bermuda grass. An eosinophilia of 5 per cent was present. The nose and throat clinic reported congestion of the turbinate on both sides. The examination of the chest, which was made during an interval between attacks, showed slight hyperresonance. The auscultation was normal. The patient received one roentgen-ray treatment over the spleen on October 11. The following day, marked eczema developed over the irradiated area, which had thus far been normal in appearance. The condition on the skin disappeared after two days. On March 3, 1928, the mother reported that the child had been feeling much better, and that he had had only one slight attack, which occurred in November. He could eat eggs and was no longer affected by the odor of mustard. The skin had been clear since the treatment.

CASE 85—New, a girl, aged 7, had had attacks of asthma for three years. They were usually brought on by damp weather, and always occurred when the child approached the furnace in the basement. The family history was negative regarding allergy.

The examination, which was made during the interval between attacks, revealed marked pharyngitis, several enlarged submaxillary glands and chronic maxillary sinusitis. This diagnosis was confirmed by a consultation with a specialist on diseases of the nose and throat. The chest was normal, but the roentgenogram showed a marked bilateral tracheobronchial adenopathy. There was no evidence of enlargement of the thymus. The skin tests were negative, however, a former examination at another institution had revealed sensitiveness to dog hair, cat hair and goose feathers. There was an eosinophilia of 2 per cent. The patient was given roentgen-ray treatment over the spleen on Nov 22, 1927. The following day the child developed a slight attack of asthma. On March 12, 1928, she was reexamined. She has not had any attacks since the treatment.

COARCTATION OF THE AORTA *

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Coarctation of the aorta signifies a constriction of the aorta in the region of its juncture with the ductus arteriosus or its vestige. The term, congenital stenosis of the isthmus, is also employed. The advantage of this term is that it is, as King¹ has remarked, more easily understood by persons who do not read English readily. The disadvantages outweigh this, for the term is clumsy and subject to ambiguous abbreviation. Many authors have maintained that the condition develops after birth. The anatomic isthmus is that part of the aorta between the origin of the left subclavian and the mouth of the ductus arteriosus, this definition excludes the large number of cases reported in which the constriction is distal to the insertion of the ligamentum arteriosum. However, in 1839, Mercier² wrote "coarctation" in French, ten years later Diesterweg,³ "coarctatio" in Latin, and the English word coarctation has an honorable history of fifty-two years.

According to Barié⁴ and others, the first case definitely described was recorded by Paris in 1791. An idea as to the incidence of coarctation may be gained from the statistics of a large number of necropsies. If conclusions may be drawn from the figures in table 1, coarctation occurs once in about 1,550 cases. Of about 200 cases in adults already reported, only nineteen were definitely recognized during life, although obstruction of the thoracic aorta was diagnosed in six additional instances. These facts can mean only that the anomaly is frequently overlooked or unrecognized.

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, December, 1927.

1 King, J T, Jr. Stenosis of the Isthmus (Coarctation) of the Aorta and Its Diagnosis During Life, *Arch Int Med* **38** 69 (July) 1926.

2 Mercier, A. Retrecissement avec obliteration presque complete de la portion thoracique de l'aorta, *Bull et mem Soc anat de Paris* **14** 158, 1839.

3 Diesterweg, C A. De aortae obliteratione singulari modo involutionis ductus arteriosi. Botalli perfecta. Berolini, G Schrade, 1849, p 40.

4 Barié, E. Du retrecissement congenital de l'aorte descendante, *Rev med* **6** 342-366, 409-442 501-516, 1886.

DEVELOPMENT

A discussion of this subject can be made more intelligible through an epitome of the early development of the vascular system¹¹ At the 3 mm stage, two aortas leave the aortic sac and are continued caudad through the first pair of branchial arches as the dorsal aortas, which communicate with the placenta The first arches are moored by the first pharyngeal pouches, and the disproportionate growth of the adjacent structures demands a more direct communication between the heart and the dorsal aortas, thus the fusion of sprouts from the aortic sac and from the paired aortas form the successive branchial arches, as the first two pair disappear Meanwhile through expansion and growth, fusion of the dorsal aortas progressing cephalad has begun The pulmonary arch on each side arises from the caudal wall of the aortic sac, and it may open into the aorta at a distinct interval from the fourth arch, close to it, or with it (fig 1)

TABLE 1—*Coarctation Revealed at Necropsy as Reported in the Literature*

| | |
|----------------------------------|------------------------------|
| Lochte ⁵ | 4 in 10,000 (approximately) |
| Fawcett ⁶ | 18 in 22,316 |
| Jaffe and Sternberg ⁷ | 1 in 4,500 |
| Meixner ⁸ | 16 in 21,481 |
| Hansteen ⁹ | 4 in 10,000 (approximately) |
| Ophuls ¹⁰ | 1 in 3,000 |
| Total | 44 in 68,300 (approximately) |

At this period the seventh cervical segmental arteries, which will largely form the subclavians, spring from the dorsal aspect of the unpaired aorta Apparently because its largest branch, the vertebral, is fixed by the cervical vertebrae, each subclavian moves cephalad on to its respective dorsal aorta and ascends it when the aortas are pulled caudad

5 Lochte, quoted by Reinitz Ueber congenitale Stenose und Obliteration am Isthmus aortae, Kiel, Schmidt und Klaunig, 1908

6 Fawcett, J Coarctation of the Aorta as Illustrated by Cases from the Postmortem Records of Guy's Hospital from 1826-1902, Guy's Hosp Rep **59** 1, 1905

7 Jaffe, R H, and Sternberg, Herman Kriegspathologische Erfahrungen, Virchows Arch f path Anat **231** 346, 1921

8 Meixner, Karl Berstung der aufsteigenden Korperschlagader bei Verschluss am Ende des Bogens, Beitr z gerichtl Med **5** 72, 1922

9 Hansteen, E H Medfødt aorta-stenose, Norsk Mag f Laegevidensk **86** 1073 (Oct) 1925

10 Ophuls, W A Statistical Survey of Three Thousand Autopsies from the Department of Pathology of the Stanford University Medical School, Univ Ser Med Sc, Palo Alto **1** 131, 1926

11 Congdon, E D Transformation of the Aortic-Arch System During the Development of the Human Embryo, Contrib Embryol, Carneg Inst, Washington **14** 47, 1922

with the descent of the heart into the thorax, it is not until the end of the seventh week (18 mm stage) that the left subclavian reaches its definitive position close to the origin of the left common carotid. By the 14 mm stage however, the aortic sac has been divided into the definitive aorta and pulmonary trunk, and the breaking up of the branchial arch system is now effected rapidly, principally by atrophy of four parts of the vascular system: the segment of each dorsal aorta between the third and fourth arches, the caudal end of the right paired aorta, and the distal part of the right pulmonary arch. Congdon attributes these interrup-

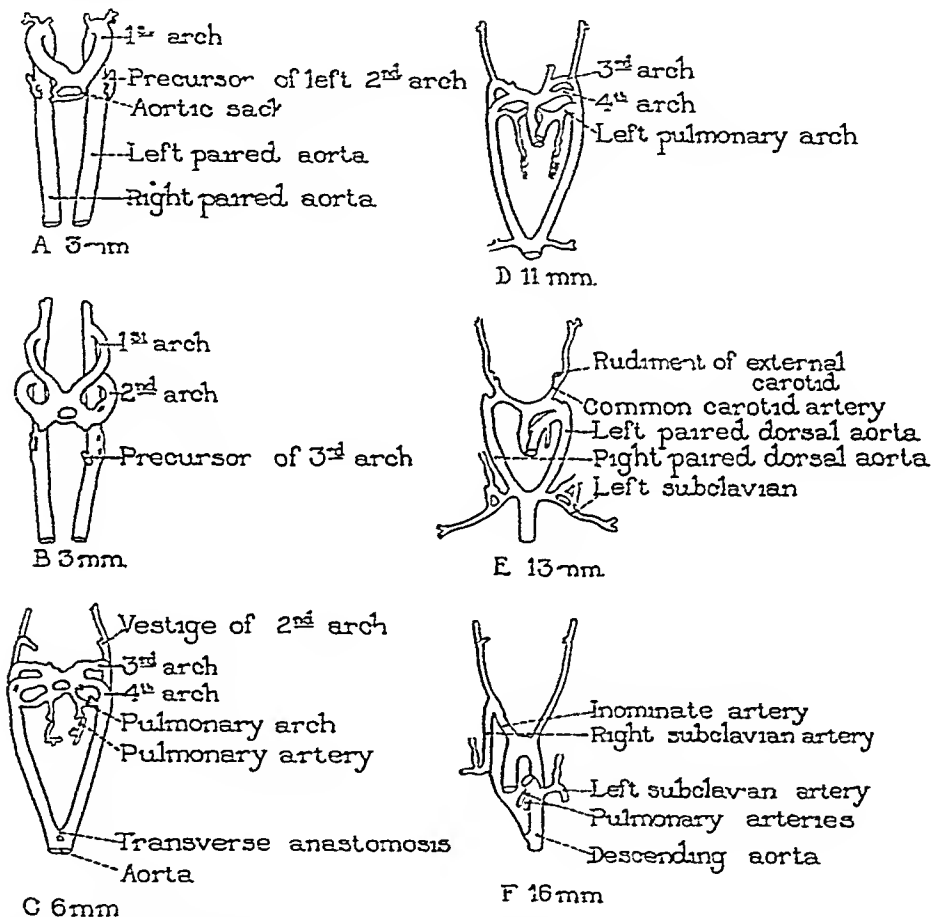


Fig 1—The development of the aortic-arch, drawn from reconstructions (After Congdon)

tions to reduction of the blood-flow through the affected segments. In specimens studied by him, he described the changes as follows:

The fourth arch region, which was at the summit of the forming definitive arch, sinks to the descending limb, and the region of the left common carotid, now shared by the innominate, comes to constitute the entire summit. The region of the arch derived from the fourth arch increases rapidly in diameter to reach in cross-section an approximate equality with the more proximal and distal parts derived from vessels which are already capacious at the beginning of the branchial period.

The fourth arch is, however, usually considered to have been the primordium of the isthmus

The interventricular septum is completed by the end of the second month and no further radical change takes place in the cardiovascular system until the obliteration of the ductus arteriosus after birth. In 1826, Kilian¹² first announced that this was effected through the change in blood pressure due to the expansion of the lungs. In 1852, Rokitansky¹³ stated that the ductus was obliterated through an uneven proliferation of the intima. Schaeffer and Radasch¹⁴ recently corroborated this, and attribute it to the atrophy of disuse, as is found in other parts of the body. Walkhoff¹⁵ and Lange¹⁶ showed that fibers from the ductus do not normally extend into the walls of the aorta, Bartels¹⁷ interpreted this to mean that they never do.

PATHOGENESIS

Reynaud¹⁸ (1828) considered coarctation a persistence of the fetal state in some way influenced by the involution of the ductus. Rokitansky¹³ (1852) was in essential agreement. In 1887, Loriga¹⁹ maintained that the ductus arteriosus did not play a part in the pathogenesis, and that the anomaly could be traced back to intra-uterine life, the differing pathologic types corresponding to the differing periods at which the lesion began. Dickinson and Fenton,²⁰ Minkowski,²¹ Monckeberg²² and Meixner⁸ believe it is of developmental origin. Meixner considers the atherosclerotic changes so often found in the aorta usually proximal but sometimes just distal to the stenosis owing to the

12 Kilian, quoted by Klotz. *Tr. A. Am. Phys.* **22** 213, 1907

13 Rokitansky, quoted by Barié (footnote 4), by Bonnet. *Rev. de med.* 1903, vol. 23, by Klotz (footnote 12), by Sankott. *Anat. Anz.* **48** 261, 273, 1915

14 Schaeffer, J. P., and Radasch, H. E. On the Obliteration of the Lumen of Blood Vessels, the Origin and Nature of the Mass which Comes to Occupy the Lumen of an Artery Segment Between Two Ligatures, *Am. J. Anat.* **33** 219, 1924

15 Walkhoff, quoted by Knierim. *Ein Fall von Stenose der Aorta in der Gegend der Insertion des ligamentum arteriosum*, Marburg, 1880, p. 1, by Bartels. *Hospitalstid.* **5** 1549, 1912

16 Lange, quoted by Knierim and by Bartels (footnote 15)

17 Bartels, C. D. *Et tilfaelde af stenosis aortae congenita*, *Hospitalstid.* **5** 1549, 1912

18 Reynaud, quoted by Knierim (footnote 15, first reference), Barié (footnote 4), Bonnet (footnote 13, second reference) and others

19 Loriga, G. *Stenosi ed oblitterazione congenita dell' aorta*, *Riv. clin. di Bologna* **7** 529, 1887

20 Dickinson, W. L., and Fenton, W. J. A Case of Complete Coarctation of the Arch of the Aorta, Necropsy, *Lancet* **2** 1196, 1900

21 Minkowski, Oscar. *Ein Fall von Stenose der Aorta an der Einmündungsstelle des Ductus Botalli (isthmus aortae persistens)*, *München med. Wchnschr.* **48** 1335, 1901

22 Monckeberg, quoted by Lutzow-Holm. *Norsk Mag. f. Laegevidensk.* **86** 1066 (Oct.) 1925

overdistention of the vessel, which experiences a tug at each fixed point, such as the origin of the intercostals, but especially at the insertion of the ligamentum arteriosum

The prenatal development of coarctation in all cases has never been universally accepted. Kaufmann,²³ Zenoni²⁴ and others attribute it in some cases at least to the propagation of an inflammatory process in the ductus botalli to the walls of the aorta. In 1844, Hamernjk²⁵ observed that the constriction might be proximal to, at the site of, or distal to, the aortic opening of the ductus arteriosus, and accordingly divided these cases into three types, he accepted Reynaud's theory for the first, but seems to have supposed that prolongation of the thrombus hypothesized in the closure of the ductus was responsible for the other two forms. In 1855, Skoda²⁶ argued that fibers from the ductus extended into the aortic wall, and that these fibers contracted with the contraction of the ductus in the process of its obliteration. In 1900, Schlesinger²⁷ revived the theories of both Reynaud and Skoda. Three years later, Bonnet²⁸ elaborated these two hypotheses. In fact, according to Bonnet, constriction of the aorta proximal to the mouth of the ductus arteriosus dates from intra-uterine life and, if not a transient persistence of the normal fetal state, is incompatible with life for more than a brief period. On the other hand, constriction at or distal to the ductus he explains by Skoda's theory, and finds it devoid of influence on the health or longevity of the person except that it may predispose to endocarditis. He called these, respectively, the infantile ("type du nouveau-ne") and the adult types. Abbott²⁹ offered this explanation in 1927.

It has been intimated several times³⁰ that syphilis may cause coarctation, but striking arguments have not been adduced in support of the theory.

23 Kaufmann, Eduard. *Lehrbuch der speziellen pathologischen Anatomie*, ed 8, Berlin, Georg Reimer, 1922, vol 1, pp 69-70.

24 Zenoni, C. Occlusione completa dell' aorta discendente, *Arch per le sc med* **35** 1, 1911.

25 Hamernjk, quoted by Diesterweg (footnote 3), by Knierim (footnote 15, first reference) and others.

26 Skoda, quoted by Knierim (footnote 15, first reference), by Barie (footnote 4), by Bonnet. *Rev de med*, 1913, vol 23, and by others.

27 Schlesinger, Hermann. Stenosis of the Aorta Near the Duct of Botalli, *Internat Clin* **4** 140, 1900.

28 Bonnet, L. M. Sur la lesion dite stenose congenitale de l'aorte dans la region de l'isthme, *Rev de med* **23** 108-126, 255-265, 335-353, 418-438, 481-502, 1903.

29 Abbott, M. E. Coarctation of the Aorta. Hypoplasia of the Aorta and Its Branches, Anomalies of the Aortic Arch, in Osler and McCrae, *Modern Medicine*, ed 3, Philadelphia, Lea & Febiger, 1927, vol 4, pp 772-794.

30 Edelmann, A, and Maron, R. Die Isthmusstenose der Aorta und ihre Differentialdiagnose, *Wien Arch f inn Med* **4** 1 (April) 1922. Koster and Forselius. Fall af total stenosis aorta, *Hygeia* **77** 935, 1915.

PATHOLOGY

Bonnet's division into the infantile and adult types simplifies discussion of the pathology of coarctation. As found in fetuses, stillborn and young infants, coarctation is usually a diffuse narrowing of the isthmus of the aorta, but this segment may be represented by a fibrous cord or be altogether lacking. The ductus is patent in almost inverse ratio to the lumen of the isthmus, and where the latter is atresic, the pulmonary trunk is continued with undiminished diameter into the descending aorta. With one exception,⁸ there is no collateral circulation. Grave developmental defects of the cardiovascular system in other parts of the body are common.

The aorta in the case of adults (and occasionally of infants dying from other causes) appears as though it had been more or less tightly ligated at or just distal to the ductus arteriosus, which is usually distal to the origin of the left subclavian but is in a few cases proximal. The ductus, which is usually obliterated, fixes the contiguous part of the aortic wall and may even appear to draw it toward the heart. Exceptions to this general type occur. The heart may be normal in every way, developmental anomalies other than bicuspid aortic valves are comparatively rare. Hypertrophy is present in about three fourths of the cases, but is associated in some of these with valvular disease, which may have caused the hypertrophy. The ascending aorta is often dilated to a varying degree and may be the seat of aneurysm, and sometimes there is an aneurysm distal to the stenosis, rupture is not infrequent. The aortic wall is at times thicker than normal, but usually is thinner. The inner surface may be normal, or it may show any degree of arteriosclerosis, sometimes with extensive calcification. Syphilitic change is infrequent. In some cases, there is slight gradual diminution of the caliber of the arch proximal to the lesion, in others, it remains unchanged up to the zone of stenosis. In a few instances, there appears to have been a double constriction. The degree of narrowing varies up to obliteration, and there is no characteristic picture of the inner aspect of the stenotic zone. When atresia is found, the intima lining the two blind sacs may appear normal, the occlusion may involve only the inner coats of the aorta, but more often the whole wall is apparently included. When a membranous wall stretches across the lumen, it may be perforated. The intima lining the sharply defined stricture may appear normal, but atheromatous change and even calcification, as well as scar tissue in the wall, have been found here. The descending aorta is often dilated just beyond the constriction, and it may return to its normal size distally; but more often it is somewhat smaller, probably on account of reduced blood pressure. In twenty cases, the whole aorta was hypoplastic. Just below the stenosis, there may be a variable degree of arteriosclerosis,

but more often the inner surface is clean. Bacterial endocarditis is common and sometimes associated with it is aortitis, which may be localized to the area of stenosis or just beyond. Except for aneurysms, especially of the cerebral arteries, which Turnbull³¹ has shown are of developmental origin in nonsyphilitic young persons, other significant anomalies of the vascular system are rare, and defects of importance elsewhere even rarer.

A few cases of the infantile type have been reported in young children and even in older ones, but such subjects have usually been chronic invalids. The site of the stenosis has also been reported proximal to the ligamentum arteriosum in the instance of one robust adult.³²

The collateral circulation is carried on chiefly through the anastomoses between branches of the subclavians and the aortic intercostals, the epigastric arteries sometimes contribute. Although the internal mammaries are of great importance as collateral channels and in some cases, notably those of Weber,³³ and Josefson,³⁴ seemed to have been the only dilated arteries, of others it has been remarked that they were not especially enlarged. Clinically, the enormous size of the artery along the vertebral border of each scapula is significant.

Microscopic study of the stenosed area itself has revealed little besides connective tissue. Reimtz³⁵ found the muscular and elastic layers of the aorta intact in two cases. The most thorough microscopic studies of the wall of the aorta have been made in cases of its rupture. Bronson and Sutherland,³⁶ Smith and Targett,³⁷ Bumke,³⁸ Oberndorfer,³⁹ Franckel⁴⁰ (two cases), Sella⁴¹ (two cases), Meixner⁸ (four cases) and Binder⁴² believe that diminution of elastica with replacement by

31 Turnbull, H. M. Alterations in Arterial Structure and their Relations to Syphilis, *Quart J Med* **8** 201, 1915.

32 Knierim, H. P. Ein Fall von Stenose der Aorta in der Gegend der Insertion des ligamentum arteriosum, Marburg, 1880, p. 1.

33 Weber, F. P. Stenosis (co-arcuation) of the Aortic Isthmus, with Sudden Death from Rupture of a Cerebral Aneurysm, *Proc Roy Soc Med (Sect Med)* **20** 29 (June) 1927.

34 Josefson, A. Stenosis isthmus aortae, *Hygiea* **3** 131, 1903.

35 Reimtz, O. Ueber congenitale Stenose und Obliteration am Isthmus aortae, Kiel, Schmidt & Klaunig, 1908.

36 Bronson, E., and Sutherland, G. A. Ruptured Aortic Aneurysms in Childhood, with the Report of a Case, *Brit J Child Dis* **15** 241, 1918.

37 Smith, F. J., and Targett, J. H. Aneurysm of the Aorta in a Boy Aged Nine Years, *Tr Path Soc London* **48** 53, 1896-1897.

38 Bumke, quoted by Meixner (footnote 8), by Abbott (footnote 29).

39 Oberndorfer, quoted by Meixner (footnote 8).

40 Fränckel, P. Präparate von spontanen Aortenrupturen, *Berl klin Wchnschr* **1** 795, 1913.

41 Sella, quoted by Meixner (footnote 8) and by others.

42 Binder, A. Zur Kasuistik der sogenannten Spontanenruptur der Aorta ascendens, *Med Klin* **15** 1091, 1919.

connective tissue is the essential feature Oppenheim,⁴³ on the other hand, considered the aorta in his case essentially normal both grossly and histologically Judging by experiments and observation at necropsies on aviators fallen from great heights, he believes that spontaneous rupture of a normal aorta may occur from a sudden increase in pressure in the region of the greatest stretching of the wall and of highest pressure, that is, of the under surface of the arch These divergent views may be reconciled through the work of Turnbull,³¹ who has found in the aortas of young persons without syphilis or abnormally high blood pressure occasional areas of focal degeneration in the media apparently originating in the rupture of the elastica The initial break was presumably due to pressure, especially since such areas are found at the site of complete rupture independent of inflammation or degeneration He believes the development of the aorta in such cases is relatively or absolutely insufficient

Constriction of the aorta beyond the usual site has been reported by Schlesinger,⁴⁴ Quain,⁴⁵ Power⁴⁶ and Latile⁴⁷ Roussy and L'Hermitte⁴⁸ have reported a case of thrombosis of the aorta distal to the renal arteries, which did not result fatally, the diagnosis was later corroborated at necropsy Achard, Leblanc and Rouillard⁴⁹ found reports of only two such cases The diagnosis in one case was purely clinical, and study of the original article suggests that it may have been coarctation, the other report was not available

DIAGNOSIS

Coarctation of the infantile type has been diagnosed only once (in a child, aged 3)⁵⁰ It is of little practical importance that it should be diagnosed, since such patients are doomed to an early death Coarctation of the adult type has been diagnosed clinically in four children⁵¹

43 Oppenheim, Franz Gibt es eine Spontanenruptur des gesunden Aorta und wie kommt sie zustande? Munchen med Wchnschr **45** 1234, 1918

44 Schlesinger, quoted by Erman Berl klin Wchnschr **10** 217, 1873

45 Quain, R Partial Contraction of the Abdominal Aorta, Tr Path Soc London **1** 244, 1848-1850

46 Power, quoted by Bonnet (footnote 28)

47 Latile Athérome et obliteration partielle de l'aorte, bruit de galop, mort par asystolie, Bull et mém Soc anat de Paris **3** 40, 1878

48 Roussy and l'Hermitte, quoted by Aubertin M Press & Circ **124** 221, 1927

49 Achard, C, Leblanc, A, and Rouillard, J Trois cas d'oblitération de l'aorta, Bull et mém Soc méd d hôp de Paris **44** 903, 1920

50 Carpenter, George On Congenital Heart Affections, Especially in Relation to the Diagnosis of Various Malformations, Proc Roy Soc Med **2** 275, 1908-1909

51 Carpenter (footnote 50) Ciaglinski, K Przypadek wrodzonego zwężenia aorty, Gaz lek **14** 740, 1894 Hochsinger, quoted by Bonnet (footnote 28), by Lommel Med Klin **15** 892, 1919 Weigert, R Ueber einen Fall von angeborener Stenose der Aorta an der Einmündung des Ductus arteriosus Botalli, Allg med Centr-Ztg **74** 1, 1905

In 1835 Legrand ⁵² and in 1839 Mercier ² diagnosed an obstruction to the thoracic aorta, but Oppolzer ⁵³ was the first to make a diagnosis of coarctation at the site of election, he did this twice and saw the diagnosis verified post mortem both times. Little or nothing has been added to Oppolzer's diagnostic criteria.

In the clinical diagnosis of coarctation, precordial murmurs are of little consequence, as they are sometimes absent, they may be caused by superimposed endocarditis, and, finally, they have been described in such a variety of terms that nothing pathognomonic can be deduced. The murmur in the interscapular space, more often to the left of the vertebral column, is of greater importance. Oppolzer attributed this to the stream of blood rushing through the greatly enlarged superior intercostal artery (intercostalis suprema). Walshe, according to Dickinson and Fenton, ²⁰ attributed it to blood passing through the stenosed area, and thought that its absence would prove atresia. The data are insufficient to determine this point. A murmur in the same position may be caused by a patent ductus arteriosus, but distinguishing the two conditions, unless associated, should not cause trouble. The presence of enlarged superficial arteries of the neck and thorax (especially of the dorsal scapulars), over all of which bruits and thrills may be heard, is usually the outstanding feature. However, in 1920 Woltman and Shelden ⁵⁴ diagnosed the condition on the basis of absence of pulsation in the abdominal aorta and femorals. More recently in one of his cases Laubry ⁵⁵ verified post mortem the diagnosis made on such grounds, he believes that marked disproportion in the blood pressure of the brachial and femoral arteries is enough basis for the diagnosis. The blood pressure in the arm is often elevated, and in most cases the pulse pressure is also high. The electrocardiograph does not show any important or constant change, as Heynsius van den Berg, ⁵⁶ King ¹ and others have remarked. Roentgenologic examination of the thorax is of value in excluding aneurysm, which has been the most common erroneous diagnosis, but the presence of aneurysm does not exclude coarctation. The roentgenogram is also of some value in excluding intrathoracic neoplasm. However, I have been able to find but one case ⁵⁷ in which such a tumor caused collateral

52 Legrand, quoted by Barie (footnote 4)

53 Oppolzer, quoted by Diesterweg (footnote 3), by Barie (footnote 4)

54 Woltman, H. W., and Shelden, W. D. Neurologic Complications Associated with Congenital Stenosis of the Isthmus of the Aorta: a Case of Cerebral Aneurysm with Rupture and a Case of Intermittent Lameness Presumably Related to Stenosis of the Isthmus, *Arch Neurol & Psychiat* **17** 303 (March) 1927

55 Laubry, Charles. Discussion in Bull et mem Soc med d hôp de Paris **50** 1725, 1926

56 Van den Berg, M. R. H. Stenosis Isthmi Aortae, *Nederl Tijdschr v. Geneesk* **2** 773, 1911

57 Seed, London. Personal communication from the author

circulation, and in one instance⁹ of moderate stenosis a sarcoma of the mediastinum was associated. Louga¹⁹ advanced the original idea that exophthalmic goiter must be considered in the differential diagnosis on account of the bruits and thrills in the neck, but heretofore this point has not been emphasized.

When cardiac failure has been the most prominent factor, coarctation has been thought of a few times but discarded because evidence of collateral circulation was not found, however in most of these cases, aortic aneurysm has been diagnosed. In a number of instances, subacute bacterial endocarditis has overshadowed the picture. Some persons with this abnormality have died suddenly or from causes not related to the cardiovascular system.

COARCTATION DIAGNOSED DURING LIFE

The clinical diagnosis of coarctation has been reported twenty-two times according to Bailié,⁴ Bonnet,²⁸ Hirschfelder,⁵⁸ Meixner,⁸ and King.¹ In addition, the following authors have reported the clinical diagnosis of coarctation on thoroughly adequate grounds: Babonneix, Oury and Widiez,⁵⁹ S. D. Blackford,⁶⁰ Brown,⁶¹ Deneke,⁶² Edelmann and Maron,³⁰ van den Berg,⁷⁶ King (five cases),⁶³ Kovesi,⁶⁴ in addition to the case examined at necropsy), Laboulbene and Claisse,⁶⁵ Laubry,⁵⁵ (two cases), Lommel,⁶⁶ Oppenheimer,⁶⁷ Parsons-Smith,⁶⁸ Pel,⁶⁹ Pilod and Hugonot,⁷⁰ Reichel,⁷¹ Schlesinger,²⁷ Stirling,⁷² Stuijs-

58 Hirschfelder, A. D. *Diseases of the Heart and Aorta*, Philadelphia, J. B. Lippincott Company, 1918, p. 556.

59 Babonneix, L., Oury and Widiez. *Rétrecissement congénital de l'aorte et syndrome hémogénique*, Bull. et mem. Soc. méd. d. hôp. de Paris **51** 866 (June 16) 1927.

60 Blackford, S. D. Personal demonstration.

61 Brown, Alexander. *Congenital Stenosis of the Aorta*, Lancet **1** 1719, 1912.

62 Deneke, Theodor. *Zur Klinik der Isthmusstenose der Aorta*, Virchows Arch. f. path. Anat. **254** 336, 1925.

63 King, J. T., Jr. *Clinical Aspects of Congenital Anomalies of the Aorta*, Am. Heart J. **2** 144 (July) 1926, also footnote 1.

64 Kovesi, G. *Stenosis Isthmus Aortae*, Orvosi hetil. **1** 1055, 1906.

65 Laboulbene, A., and Claisse, P. *Rétrecissement congénital de l'aorte descendante, a sa partie supérieure, vers l'abouchement du canal artériel*, Bull. et mem. Soc. méd. d. hôp. de Paris **7** 945, 1890.

66 Lommel, F. *Ueber Stenose des Aortenisthmus*, Med. Klin. **15** 892, 1919.

67 Oppenheimer, B. S. Personal communication from the author.

68 Parsons-Smith, B. T. *Case of Congenital Aortic Atresia*, Proc. Roy. Soc. Med. **14** 73, 1921.

69 Pel. *Isthmus stenose*, Nederl. Tijdschr. v. Geneesk. **1** 2032, 1908.

70 Pilod and Hugonot. *Double rétrécissement congénital de l'aorte a son origine et au niveau de l'isthme*, Bull. et mem. Soc. med. d. hop. de Paris **1** 1719, 1926.

berg,⁷³ Langmead, Weber and Gossage,⁷⁴ Weber and Price⁷⁵ and Werley,⁷⁶ Coarctation has therefore been believed to be present, although not verified by necropsy, at least fifty times. Pilod and Hugonot did not find evidence of collateral circulation over the thorax. In the case reported by Weber and Price, the patient died from external rupture of an aneurysm of the right subclavian artery. A definite history of intermittent claudication was given in Heynsius van den Berg's case, and in one of King's, Parsons-Smith's patient had "a functional incapacity of the lower limbs, especially noticeable after resting." Cramps in the legs were not common.⁷⁶ Edelmann and Maron's patient had muscular arms but poorly developed legs. Some hypertrophy of the heart was found roentgenologically in five cases,⁷⁷ roentgenologic examination of the heart was negative in five.⁷⁸ The electrocardiogram was essentially negative in eight cases.⁷⁹ The stenosis was considered proximal to the origin of the left subclavian artery by Brown, Deneke and Stursberg. Coarctation has been definitely diagnosed in life and verified post mortem nineteen times,⁸⁰ a tentative diagnosis was made twice,⁸¹ and an obstruction of the thoracic aorta was diagnosed six times.⁸²

71 Reichel, O. Ein Fall von Isthmusstenose der Aorta, Allg. Wien. med. Ztg. **46** 268, 1901.

72 Starling, H. J. Coarctation of the Aorta, *Lancet* **1** 1317, 1920.

73 Stursberg, H. Sphygmographische Befunde bei Verengerung der Aorta am Isthmus, *Deutsches Arch. f. klin. Med.* **107** 33, 1912.

74 Langmead, Frederick. A Case of Thoracic Aneurysm Not Connected with the Aorta, *Proc. Roy. Soc. Med.* **5** 194, 1912, discussion by F. P. Weber, Gossage, A. M. Case of Coarctation of the Aorta, *Proc. Roy. Soc. Med.* **6** 1, 1912.

75 Weber, F. P., and Price, F. W. Coarctation of the Aorta in an Adult with Death Due to Rupture of an Aneurysm in the Neck, *Lancet* **2** 692, 1912.

76 Werley, G. Aortic Hypoplasia and Isthmus Stenosis. Case Reports, *Texas State J. Med.* **23** 285 (Aug.) 1927.

77 Deneke (footnote 62). Edelmann and Maron (footnote 30, first reference). Van den Berg (footnote 56). King (footnote 63). Pilod and Hugonot (footnote 70).

78 King (footnote 1). Starling (footnote 72). Werley (footnote 76).

79 Deneke (footnote 62). Van den Berg (footnote 56). King (footnotes 1 and 63). Parsons-Smith (footnote 68). Pilod and Hugonot (footnote 70).

80 Abbott (footnote 29). Bahn, Karl. Ueber isolierte Dextrocardie mit Isthmusstenose der Aorta und Endocarditis lenta, *Deutsches Arch. f. klin. Med.* **166** 297 (March) 1925. Barie (footnote 4). Bonnet (footnote 28). Gossage, A. M. Coarctation of the Aorta, *Proc. Roy. Soc. Med.* **2** 210, 1909. Laubry (footnote 55). Maixner, Emerich. Vrozene sužení srdečnice poblíže provodu Botallova. Sužení otvoru tepenného levoho, nedomykavost chlopni měsíčitych aorty a dvojípove, *Čas. lek. česk.* **17** 201, 209, 1878. Umber. Aortenstenose und Isthmusenge der Aorta, *München. med. Wchnschr.* **53** 96, 1906. Weinberger, Maximilian. Isthmusstenose der Aorta, kombiniert mit offenen Foramen ovale, *Deutsche med. Wchnschr.* **35** 512, 1909, Weitere Beiträge zur Radiographie der Brustorgane, *Med. Klin.* **4** 584, 1908.

CASES OF COARCTATION AS FOUND IN THE INFANT
AT NECROPSY

This series, which does not include reports abstracted by Baillé, Bonnet, or Abbott may be presented most conveniently in two groups

Group 1 includes uncomplicated examples of the infantile type, in which the aorta is narrowed between the origin of the left subclavian and the mouth of the ductus arteriosus, the ductus is patent and supplies varying amounts of blood to the descending aorta. Cases have been reported by Audry,⁸³ Borissowa,⁸⁴ Carpenter (two cases),⁸⁵ Cautley,⁸⁶ Essard,⁸⁷ Gibert,⁸⁸ Hoche and Morlot,⁸⁹ Holt,⁹⁰ Kolisko,⁹¹ Meixner,⁸ Morlot and Vermelin,⁹² Nagel,⁹³ Sankott⁹⁴ and Strassmann⁹⁵ (two cases). One subject died⁸⁴ from diphtheria at the age of 18 months, another from⁹⁴ bacterial endocarditis at 3 years, the remaining thirteen died in less than one year, bronchopneumonia being the terminal event in six. In six cases, the family history was said not to be significant, and the infant was born at full term. Cyanosis was mentioned as present in three cases and absent in six. Imperfect closure of the interauricular

81 Josefson (footnote 34) Knerim (footnote 32)

82 Abbott, M. E. Coarctation of the Aorta, *Am Heart J*, to be published

83 Audry, J. Retrecissement de l'isthme de l'aorte chez un nouveau-ne, *Lyon med* **106** 161, 1906

84 Borissowa, A. P. Zwei Falle von Stenosis isthmi aortae, *Medizinskoje Obozrenije*, LXXIV, no 13, abstr, *Zentralbl f allg Path u path Anat* **22** 379, 1911

85 Carpenter, George. Three Cases of Congenital Heart Disease, *Brit J Child Dis* **5** 396, 1908

86 Cautley, E. Two Specimens of Congenital Heart Disease (1) Stenosis of the Isthmus Aortae with Patent Ductus Arteriosus and Patent Interventricular Septum, *Proc Roy Soc Med* **2** 34, 1908-1909

87 Essard. Malformation congenitale de l'aorte, *Lyon méd* **108** 1034, 1907

88 Gibert. Distribution anormale des arteres aorte et pulmonaire, *Bull et mem Soc anat de Paris* **14** 203, 1839

89 Hoche, L., and Morlot, R. Un cas de stenose congenitale de l'aorte chez un nouveau-ne, *Bull et mem Soc anat de Paris* **91** 91, 1921

90 Holt, L. E. Malformation of the Heart, Open Foramen Ovale and Ductus Arteriosus, Stenosis of Aorta, Hypertrophy of Both Ventricles, *New York M J* **39** 335, 1884

91 Kolisko, quoted by Meixner (footnote 8), by Woltman and Shelden (footnote 54) Abbott (footnote 82)

92 Morlot, R., and Vermelin, H. Deux cas de stenose congenitale de l'aorte chez le nouveau-ne, *Compt rend Soc de biol* **85** 1082, 1921

93 Nagel, W. Ein Beitrag zur Kasuistik uber angeborene Herzfehler, *Freiburg, Speyer and Kaerner*, 1908

94 Sankott, A. Ueber einen eigenartigen Fall von Stenose des Isthmus aortae, *Anat Anz* **48** 261-273, 1915

95 Strassmann, G. Der plotzliche Tod bei Stenose des Isthmus aortae, *Beitr z gerichtl Med* **5** 91, 1922

septum was found seven times, of the interventricular septum four times. In eleven cases, the right ventricle was hypertrophied, in six, the left ventricle.

Group 2 includes atypical examples in infants. Cases have been reported by Barrett,⁹⁶ Diesterweg,³ Dreyfuss⁹⁷ (four cases), Fisher⁹⁸ Greenfield,⁹⁹ Grieg,¹⁰⁰ Franckel,⁴⁰ von Hofsten,¹⁰¹ Hayashi,¹⁰² Herxheimer,¹⁰³ Marx,¹⁰⁴ Meixner⁸ (two cases), Pamard,¹⁰⁵ Saltykow,¹⁰⁶ Sieber,¹⁰⁷ Steidele,¹⁰⁸ Stille,¹⁰⁹ Steinberg,¹¹⁰ Vallette and Mollaret,¹¹¹ Verocay,¹¹² Volbeding¹¹³ and Waggaman¹¹⁴. The most striking fact about this group of twenty-six atypical cases is the presence of grave developmental defects not connected with the cardiovascular anomalies in eight cases,¹¹⁵ and severe cardiovascular anomalies in two of these¹¹⁶

96 Barrett, T. B. Malformation of a Foetus, *Lancet* **23** 349, 1835

97 Dreyfuss, M. Coarctation of the Aorta, Infantile Type, *Internat. A. M. Museums Bull.*, to be published

98 Fisher, Theodore. Two Cases of Congenital Disease of the Left Side of the Heart, *Brit. M. J.* **1** 639, 1902

99 Greenfield, quoted by Humphrey. Congenital Diseases of the Heart, in Allbutt and Rolleston, *System of Medicine*, New York, The Macmillan Company, 1909, p. 286

100 Grieg, quoted by Kohl. *Centralbl. f. allg. Pathol. u. path. Anat.* **20** 1089, 1909

101 Von Hofsten, S. Fall af Aortastenose, *Hygiea* **48** 19, 1886

102 Hayashi, A. Stauungslunge bei Offenbleiben des Ductus Botalli, *Monatsschr. f. Kinderh.* **11** 224, 1912

103 Herxheimer. Discussion on Stenose des Aortenbogens vor Einmündung des Ductus Botalli, *Verhandl. d. deutsch. path. Gesellsch.* **13** 205, 1909

104 Marx, Herman. Ueber einen Fall von zunehmender Stenose der Aorta vom Conus bis zur Einmündung in dem Ductus Botalli, *Worms-am-Rhein*, A. K. Boeninger, 1912

105 Pamard, quoted by Kohl (footnote 100)

106 Saltykow, quoted by Kohl (footnote 100)

107 Sieber. Demonstration von embryonalen Missbildungen am Zirkulations- und am Digestionsapparate, *Deutsche med. Wchnschr.* **35** 692, 1909

108 Steidele, quoted by Kohl (footnote 100)

109 Stille, quoted by Hirschfelder (footnote 58), by Kohl (footnote 100)

110 Sternberg-Brunn, Carl. Beiträge zur Kenntniss der angeborenen Herzfehler, *Verhandl. d. deutsch. path. Gesellsch.* **13** 198, 1909

111 Vallette, P., and Mollaret, J. Un cas de retrecissement congenital de l'aorte chez un nourisson, *Marseille med.* **42** 41, 1906

112 Verocay, Jose. Contributo alla casistica dell' artresia congenita dell' aorta in prossimita del dutto arterioso del Botallo, *Pathologic* **5** 35, 1913

113 Volbeding, quoted by Verocay (footnote 112)

114 Waggaman. Congenital Stenosis of the Aorta, *Tr. Med. Soc. Dist. Columbia* **3** 65, 1876

115 Barrett (footnote 96) Dreyfuss (footnote 97) Meixner (footnote 8) Sieber (footnote 107) Sternberg (footnote 110) Verocay (footnote 112)

116 Dreyfuss (footnote 97) Sieber (footnote 107)

and in two others¹¹⁷ Three of the subjects were stillborn and a fourth was aborted In four cases,¹¹⁸ and perhaps a fifth,⁴⁰ the constriction was distal to the mouth of the obliterated ductus arteriosus, that is, of the adult type, one of these³ subjects was but 8 days of age The right ventricle was hypertrophied in nine cases, the left in six The interauricular septum was imperfect in at least seven cases, the interventricular in four

Comment on Groups 1 and 2—To the series of eighty-two cases of coarctation in infants reviewed by Abbott,²⁹ the present series of forty-two is added In this group, there are seventeen males and sixteen females, in nine, the sex was not specified These figures agree with Manneberg's¹¹⁹ denial of the predominance in males The oldest subject was 3 years of age, only one other was more than 1 year, Abbott included none older than 1 year In sixteen cases the true anatomic isthmus was narrowed and there was no abnormality of note except in the heart, these were classical and uncomplicated examples of the infantile type The adult type was found in four cases and probably was not related to the cause of death The prolongation of the ductus arteriosus formed the descending aorta in nine cases, twenty-five were previously assembled Other cardiovascular defects were found in twenty necropsies

CASES OF COARCTATION AS FOUND IN THE ADULT AT NECROPSY

This series¹²⁰ which also does not include reports abstracted by Barié, Bonnet or Abbott²⁹ (in "Modern Medicine"), may be presented in groups

GROUP 1—In this group are classical examples of the adult type (without complications) in which constriction is at or distal to the mouth of the ductus arteriosus Cases have been reported by Bartels,¹⁷ Beneke¹²¹ Broome¹²² Edgren¹²³ Halberer¹²⁴ Hansteen⁹ (three cases),

117 Fisher (footnote 98) Stille (footnote 109)

118 Diesterweg (footnote 3) Greenfield (footnote 99) Von Hofsten (footnote 101) Waggaman (footnote 114)

119 Manneberg, quoted by Reinitz (footnote 35)

120 Dr Abbott, in her paper now in press (Abbott, M E Coarctation of the Aorta, *Am Heart J*, to be published) is including forty cases in this series, and a previously published case from the Mayo Clinic, from her own studies and seventeen cases from my abstracts, as well as six cases (Hinrichsmeyer, Libman, Nieuwejaar Oehl, Taruffi and Wadstein) found by her in the literature since this paper was completed

121 Beneke Endokarditis lenta mit Isthmusstenose, *Munchen med Wchnschr* 69 413, 1922

122 Broome, H H A Dissection Showing Abnormalities of the Veins, the Arteries and the Kidneys *Proc Anat Soc Great Britain and Ireland* 35 53, 1900-1901

Harrison,¹²⁵ Hart¹²⁶ (two cases), Josefson,³¹ Kolisko,⁹¹ Laubry,⁵⁵ Lutzow-Holm,¹²⁷ Maixner,⁸⁰ Mackenzie,¹²⁸ Murray,¹²⁹ Reinitz,³⁵ Santas,¹³⁰ Strassmann⁹⁵ and Zeoni²⁴

One subject¹²³ in this group had suffered from cardiac symptoms for twelve years, but had been incapacitated for only four weeks, four others¹³¹ had suffered from cardiac symptoms for more than a year. Otherwise their previous health had been good, it may be emphasized that one¹²⁶ was an air-pilot in the German army, although coarctation in this case was extreme. Josefson was of the opinion that his patient was afflicted with coarctation, but since he was unable to find pulsating superficial arteries during life, he hesitated to make a definite diagnosis, at necropsy, it was found that the internal mammary arteries provided the principal collateral channels. A similar case¹³² belongs in another group. Murray, Santas and Zenoni presented clinical observations sufficient for the diagnosis of coarctation, but diagnosed aneurysm of the thoracic aorta.

Habeier has reported a case of unusual interest. Three days before admission to the hospital the patient developed transverse myelitis, this caused death through complications three months later. The most striking observation at necropsy was that the anterior spinal artery had contributed to the collateral circulation and caused compression of the spinal cord at the level of the second dorsal nerves. In spite of atresia of the aorta, this woman had borne seven children. Of the women in whom atresia has been found, one died at the birth of her ninth child,⁶ and another was survived by seven children⁹⁵. In one case in which the

123 Edgren, J. G. Fall af isthmusstenose med relative aortainsufficiens, Nord med Ark, Fästband, 1897, p. 27

124 Haberer, H. Ein Fall von seltenen Collateralkreislauf bei angeborener Obliteration der Aorta und dessen Folgen, Ztschr. f. Heilk. **24** 26, 1903

125 Harrison, T. J. Singular Abnormality of the Arterial System, Constriction and Obliteration of the Aorta, etc, Penns. M. J. **3** 514, 1855-1856

126 Hart, C. Ueber die totale Obliteration des Aortenisthmus, Med. Klin. **16** 1337, 1920

127 Lutzow-Holm, G. Svaer medfødt stenose i isthmus aortae, pendselig dod, Norsk Mag. f. Laegevidensk. **85** 1066 (Oct.) 1925

128 Mackenzie, G. M. Coarctation of the Aorta with Staphylococcus Endocarditis, Am. J. M. Sc. **174** 87, 1927

129 Murray, G. R. A Case with Comments. A Case of Incomplete Coarctation of the Aorta, Necropsy, Practitioner. **72** 284, 1900

130 Santas, M. A. Estenosis congenita del istmo de la aorta en un individuo de 61 años, Rev. Soc. med. argent. **14** 17, 1906

131 Lutzow-Holm (footnote 127). Murray (footnote 129). Santas (footnote 130)

132 Erdmenger, Rudolf. Zwei Fälle von angeborenen Herzfehler mit Sektionsbefund (Pulmonalstenose bezw. Isthmusstenose), Gotting, L. Hofer, 1912

stenosis was all but complete, the patient died near the end of her second pregnancy⁹⁵ Of the women in whose cases coarctation was diagnosed clinically, one had had four children,⁵⁶ one eleven⁷⁵ and a third fourteen⁷⁴

Strassmann⁹⁵ seems to have reported the one case in which thyroidectomy had been performed, this was probably for adenomatous goiter

GROUP 2—This group includes examples of coarctation in which death was due to rupture of the aorta Cases have been reported by Berger,¹³³ Bumke,³⁸ Kolisko,⁹¹ Trevor,¹³⁴ Binder,⁴² Bronson and Sutherland,³⁶ Franckel (two cases),⁴⁰ Horder,¹³⁵ Meixner,⁸ Oppenheim,⁴³ Staunig,¹³⁶ Strassmann (four cases),⁹⁵ Smith and Targett,³⁷ Turnbull³¹ and West¹³⁷

In two cases rupture occurred through an aneurysm which was the site of vegetations, Abbott²⁹ cites a similar one, reported by Smith and Hausmann The seventeen cases of spontaneous rupture of the aorta associated with coarctation reviewed here bring the total to thirty-eight,¹³⁸ of these, thirty-one patients were men and four women, most of them were from 17 to 33 years of age Meixner attributes the striking prevalence of death from this cause in muscular males during the age of greatest effort to unusually high blood pressure produced by their energetic life or to a congenital weakness of the walls of the aorta (as Turnbull³¹ does), or more probably to a combination of these two factors In seven of these seventeen cases, it is noted that the initial symptoms appeared during or after prolonged violent exercise, death followed at once when the first break in the aortic wall was complete, or a few hours later when it became so The fact that in one¹³⁵ case the stenosis was slight and in another⁴² only moderate, lends support to the belief that the rupture was due essentially to imperfect development of the wall of the aorta In eight of this group, the ascending aorta was dilated and thin-walled, and in five¹³⁹ definite aneurysm was found Attention may

133 Berger, quoted by Meixner (footnote 8)

134 Trevor, quoted by Humphrey *Congenital Diseases of the Heart*, in Allbutt and Rolleston, *System of Medicine*, ed 2, New York, The Macmillan Company 6 286, 1909

135 Horder, T J *Dissecting Aneurysm of the Aorta in a Boy Aged Twelve, Rupture into Pericardium*, *St Barth Hosp Rep* 43 57, 1907

136 Staunig *Aortenruptur*, *Berl klin Wchnschr* 50 469, 1913

137 West *False Aneurysm with Obliteration Probably Congenital of the Aorta*, *Tr Coll Phys, Philadelphia* 2 194, 1848

138 Abbott's new series includes cases of two young men, reported by Nieuwejaar, and Wadstein, which make the total forty, in both, the aortic valve was bicuspid

139 Binder (footnote 42) Bronson and Sutherland (footnote 36) Horder (footnote 135) Kolisko (footnote 91) West (footnote 137)

also be called to the disproportion between the size and development of the upper and lower parts of the body in the case reported by West. A similar disproportion has been recorded twice,²⁹ as well as in a clinical report by Edelmann and Maron.³⁰

GROUP 3—Examples of coarctation in which death was due to cerebral hemorrhage are included in this group. Cases have been reported by Bahn,⁸⁰ Borissowa,⁸⁴ Erdmenger,¹³² Kolisko,⁹¹ Koster and Forselius,³⁰ Strassmann⁹⁵ and Weber.¹⁴⁰

Borissowa's patient was a sickly child, and in this case, aortic stenosis and coarctation were present, both in an extreme degree, but above the narrowed ostium the ascending aorta was dilated. Erdmenger's patient had suffered from mitral stenosis of rheumatic origin. Koster and Forselius' patient was syphilitic. The others of this group were healthy and robust prior to death. Definite ruptured aneurysm was mentioned by Kolisko. Strassmann and Weber. Bahn's case, which was correctly diagnosed in life has no tellow. The electrocardiogram was negative except for inverted T-waves in leads 1 and 2. At necropsy, the heart was proved to be on the right side, but the chambers were in their normal relative positions and the arch of the aorta was to the left. Inversion of other viscera was not noted. Bacterial endocarditis was also observed in this case, but the hemorrhage was independent of it. Josefson's⁹⁴ patient also suffered from endocarditis, but he died from cerebral hemorrhage secondary to embolus to the brain.

GROUP 4—The cases in this group are atypical example of coarctation. Cases have been reported by Knierim,⁸² Kohn,¹⁴¹ Kovesi,⁶⁴ Kurcysza,¹⁴² Lantinga,¹⁴³ Lesseliers,¹⁴⁴ Umber⁸⁰ and Weidman.¹⁴⁵

Knierim reported atresia proximal to the obliterated ductus, but did not emphasize this unique observation, the possibility of an error may therefore be considered. His patient was a robust middle-aged man. Kohn's case, that of a man aged 57, did not present any characteristics of coarctation either clinically or at necropsy except "marked stenosis of the isthmus with atheroma." Four other examples of¹⁴⁶ coarctation

140 Weber (footnote 33)

141 Kohn, Albert. A Case of Dilatation of the Aorta Due to Constriction at the Isthmus, *M Rec* **79** 652 1911

142 Kurcysza, A. Insufficiencia totius aortae congenita, stenosis arcus aortae, endocarditis atheromatosa. *Gaz lek* **16** 81, 1874

143 Lantinga, Freerk. Over vernauwing der aorta, Groningen, J. B. Wolters, 1874

144 Lesseliers, L. Cas remarquable de retrecissement de la crosse de l'aorte, *Ann Soc de med de Gand* **60** 45, 1882

145 Weidman, F. D. Congenital Stenosis (Coarctation) of the Isthmus of the Aorta. *Proc Path Soc Phila* **16** 78, 1914

146 Hansteen (footnote 9). Kurcysza (footnote 142). Lantinga (footnote 143). Lesseliers (footnote 144).

in which collaterals were distinctly said to be absent are included in this series, the narrowing in three of these was moderate, and in two, generalized hypoplasia of the aorta was associated. Three cases without evidence of collateral circulation at necropsy occur in Abbott's ²⁹ series. Two patients ¹⁴⁷ in this group had suffered from cardiac symptoms since birth and two others ¹⁴⁸ for about a year. The aorta was hypoplastic throughout in five cases, ¹⁴⁹ Abbott reviewed nineteen such cases in her 1927 monograph. In the literature, general hypoplasia of the aorta is less common than coarctation.

Comment on Groups 1 to 4—This series consists of fifty-seven cases in which the age was more than 3 years and in which the data are more or less adequate for statistical study. Manneberg ¹¹⁹ has denied that coarctation actually occurs more often in men than in women, and explains the apparent discrepancy by the greater number of necropsies performed on men, he estimates the ratio as 2:1. Abbott ⁸² reports cases in ninety-two males and thirty-nine females, which is in harmony with this theory, but in this additional group of fifty-seven, there were forty-seven cases in men and eight in women, which is more in keeping with the traditional view that coarctation is more common in males. In my group, eight were aged from 11 to 15 years, five from 16 to 20, fourteen from 21 to 30, and eleven from 31 to 40, as compared with four, twenty-three, thirty-two and twenty-five in the same age periods in Abbott's group. Of the fifty-seven cases reviewed by me, the aorta was obliterated in fifteen, extremely stenosed in twenty-nine, moderately stenosed in ten and slightly stenosed in one, the degree of stenosis was not given in two. That is, of 194 cases of the combined series (Abbott's revised series and mine), the diameter of the lumen of the aorta was less than 6 mm. at the site of coarctation in 151 cases. In my series, collateral circulation was said to be present in thirty-five, and not mentioned in fifteen, although it was implied in about half of these. In five cases of moderate stenosis, collateral circulation was said to be absent. The heart was enlarged in forty-four of these fifty-seven cases and not enlarged in six, among the latter, there were two cases of atresia, ¹⁵⁰ two of extreme stenosis, ¹⁵¹ in one ¹⁴⁸ of which collaterals were said to be absent, and two ¹⁵² of moderate degree. The ductus was patent in five cases, bringing the total of such cases to seventeen. Bicuspid aortic valve

¹⁴⁷ Kurcyuza (footnote 142) Lantinga (footnote 143)

¹⁴⁸ Knierim (footnote 32) Umber (footnote 80, eighth reference)

¹⁴⁹ Kovesi (footnote 64) Kurcyusza (footnote 142) Lantinga (footnote 143) Umber (footnote 80) Weidman (footnote 145)

¹⁵⁰ Franckel (footnote 40) Harrison (footnote 125)

¹⁵¹ Lantinga (footnote 143) Smith and Targett (footnote 37)

¹⁵² Hansteen (footnote 9) Horder (footnote 135)

was present in fourteen instances, thirty-one were previously reviewed⁸² In my series cerebral hemorrhage was found eight times, in three, rupture of an aneurysm was specified Simple hemorrhage is reported seven times ruptured aneurysm three times and clinical evidence of cerebral hemorrhage six times in Abbott's latest review Knierim⁸² reported an unruptured aneurysm of the basilar artery In most cases the brain was not examined post mortem, or perhaps cerebral aneurysm would have been recorded more often⁸⁴ The obvious explanation of the affection of the arteries of the brain would appear to be high blood pressure in the proximal aorta The efficiency of the internal carotid arteries in young persons however probably prevents high pressure in the cerebral arteries and this argument strengthens Turnbull's⁸¹ hypothesis that these aneurysms are rather due to inherent weakness of the arterial wall The incidence of aortic aneurysm has been mentioned Aneurysms of the left brachial in a boy and of the left vertebral have been reviewed⁸⁴ In my series death was due to cardiac failure in sixteen cases, making a total of eighty-four deaths due to this cause Subacute bacterial endocarditis was responsible for death in six cases in this series, in two, it was complicated with bacterial aortitis, endocarditis was present in another case, and in two others if infection did not cause aortic aneurysm at least infection led to rupture of the aneurysm Minor vascular anomalies, such as persistent left superior vena cava,¹⁵³ origin of the vertebral artery from the arch¹⁵⁴ and patent interauricular septum¹⁵⁵ were found in five cases in addition to the five examples of generalized aortic hypoplasia Developmental defects of consequence were found elsewhere in two cases¹⁵⁶ and minor ones in two others¹⁵⁷

GROUP 5—Miscellaneous examples of coarctation are given in this classification Moriani¹⁵⁸ has published a case that he likened to one of Monckeberg's²² the original article is not available to me Weinberger⁸⁰ demonstrated a postmortem specimen with a patent foramen ovale which is presumably from the case reported by him clinically the preceding year Jaffé and Sternberg⁷ refer to an example in a soldier dying of pulmonary tuberculosis Reports of sixteen other apparently genuine cases without adequate details have been found Eleven of these were in infants and in four of the five adult cases it was noted that coarctation was not marked and without clinical significance

153 Broome (footnote 122) Kolisko (footnote 91)

154 Haberer (footnote 124) Kolisko (footnote 91)

155 Bronson and Sutherland (footnote 36) Kohn (footnote 141)

156 Bronson and Sutherland (footnote 36) Remitz (footnote 35)

157 Broome (footnote 122) Lützow-Holm (footnote 127)

158 Moriani, G. Contributi alla patologia vasale complicazioni valvulari aortiche in stenosi congenita dell' istmo abstr Pathologia 3 241, 1911

Anders,¹⁵⁹ Langwill,¹⁶⁰ and Kurtz, Sprague and White¹⁶¹ have reported cases of moderate coarctation in which other cardiac lesions appeared to be of greater importance. In her current publication, Abbott⁸² is excluding nineteen cases of this type from her 1927 article and adding thirteen others. In fourteen of these thirty-five cases, grave developmental defects were associated with moderate coarctation, and slight coarctation complicated other minor cardiovascular anomalies in twenty-one. In fourteen instances, the ductus arteriosus was widely patent. Some of this series were complicated examples of the infantile type, four of these subjects were less than 5 years of age, but others were older. These thirty-five cases are probably not all of those published in which some degree of coarctation has been overshadowed by more serious conditions. Abbott discusses the subject in more detail in her current work and appends a bibliography.

AN UNPUBLISHED CASE OF COARCTATION WITH NECROPSY

Dr. Walter D. Shelden¹⁶² has permitted me to report a case diagnosed by him in 1906 (fig. 2). A man, aged 44, in the terminal stages of gastric carcinoma, was referred on account of an unusual cardiovascular condition. During the preceding nine months, he had suffered from cramps in the legs, which lasted a few minutes two or three times at night; he had become dizzy and had complained of palpitation and pain in the chest on exertion. He had been growing weaker, especially in the legs. The carotid arteries were markedly thickened and pulsating forcibly. Pulsation in the abdominal aorta, although the parietes were thin and relaxed, could not be felt; in the femorals it was weak and often imperceptible. The dorsal scapular arteries were tortuous and distended, and near the angle of the scapula were larger than the radial. They anastomosed with a knot of vessels near the spine. In the posterior part of the left axilla, a large artery was found in which blood was flowing downward; one branch disappeared in the ninth interspace and the other extended toward the angle of the scapula and was lost in the seventh or eighth interspace. Pressure on the left brachial stopped pulsation in both branches. Cardiac dulness was not increased. At the base, a soft blowing systolic murmur remarkable for its diffuse character was heard; this was perhaps most marked over the aortic area, but it was almost equally intense in the back to the left of the vertebral column above the level of the spine of the scapula. Atresia of the aorta just beyond the obliterated ductus was found at necropsy.

159 Anders, J. M. Sudden Death in Aortic Stenosis with Report of Two Cases, One Complicated with an Aneurismatic-Like Dilatation of the Aorta at Its Root and Marked Stenosis of this Vessel Beyond the Dilatation, *Med News* 80 872, 1902.

160 Langwill, H. G. An Unusual Cardiac Case, *Scot M & S J* 1 723, 1897.

161 Kurtz, C. M., Sprague, H. B., and White, P. D. Congenital Heart Disease. Interventricular Septal Defects with Associated Anomalies in a Series of Three Cases Examined Postmortem, and a Living Patient Fifty-Eight Years Old with Cyanosis and Clubbing of the Fingers, *Am Heart J* 3 79 (Oct) 1927.

162 Shelden, W. D. Personal communication to the author.

CASES OF COARCTATION AT THE MAYO CLINIC DIAGNOSED
CLINICALLY

CASE 1¹⁶³—In the first case so diagnosed, the patient was a woman, aged 44, who after walking suffered from precordial pressure, dyspnea tachycardia, vertigo, occasional vomiting and intermittent claudication. Pulsation in the subclavian

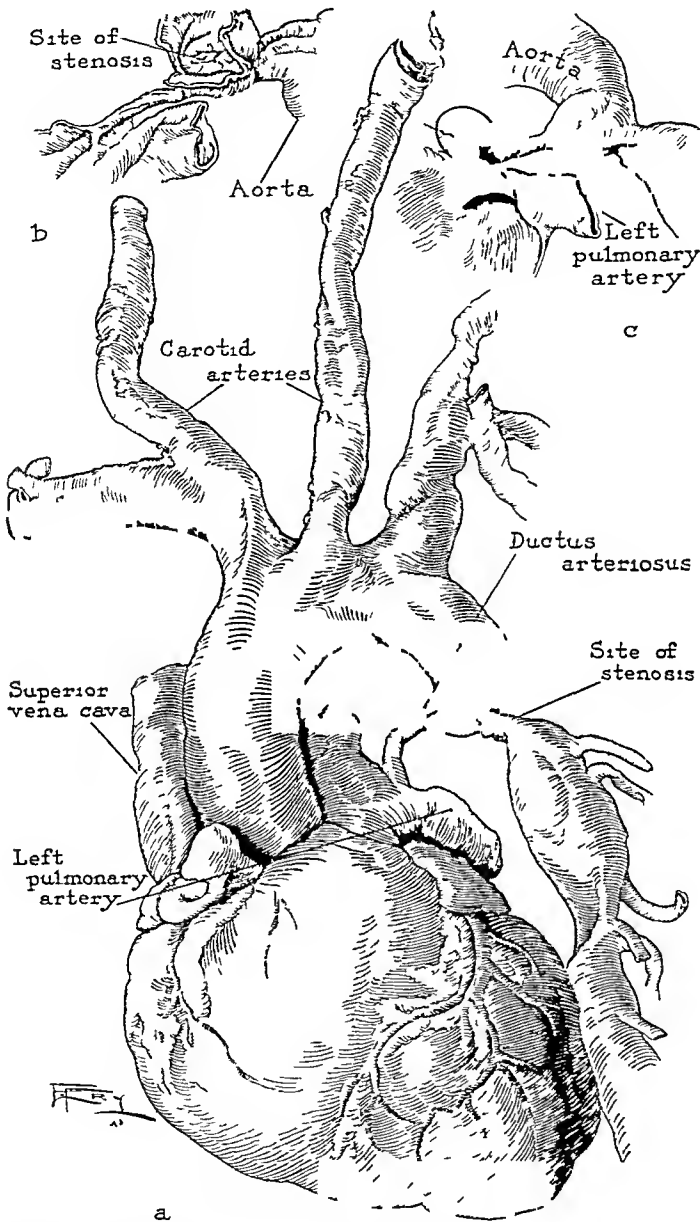


Fig 2—The heart and aorta from Shelden's case, drawn from the original specimen

and carotid arteries was strong, but other related arteries were not visible or palpable over the thorax. In contrast to the multiparas who have been cited, this woman had lost two premature infants, and perhaps had had an early miscarriage. When last heard from, her condition was unchanged.

163 Previously reported by Woltman and Shelden (footnote 54)

Comment—In one other case¹⁶⁴ diagnosed clinically, and in several diagnosed at necropsy¹⁶⁴ in which the diagnosis of coarctation was considered during life, no evidence of superficial collateral circulation was found, but postmortem examination revealed marked enlargement of the intrathoracic arteries. Lauby⁵⁵ emphasizes that pronounced disproportion of the brachial and femoral blood pressure is a sufficient basis for the diagnosis.

CASE 2¹⁶³—A robust, athletic youth, aged 20, had been in coma two days at the time of admission to the hospital. Necropsy examination confirmed the clinical diagnosis of obliteration of the aorta in the region of the insertion of the ligamentum arteriosum involving the origin of the left subclavian and hemorrhage at the base of the brain. This hemorrhage came from the rupture of a large aneurysm at the juncture of the posterior communicating and middle cerebral arteries. The heart was moderately hypertrophied and the aortic valve presented but two cusps.

CASE 3—A farmer, aged 30, was admitted to the clinic on July 31, 1925. He gave a history of a rather sudden onset of dyspnea ten weeks previously. Two weeks after the onset of the dyspnea, edema of the ankles was noticed, but it disappeared later with rest. There was no history of weakness or coolness of the legs, claudication or headache. A systolic murmur followed by a reduplicated and accentuated second sound in the second right interspace and a rough systolic murmur over the apex were heard. The physical signs of coarctation were present. Hemorrhage or exudate were not noted in the fundus. Although a moderate amount of albumin, erythrocytes and leukocytes were present in the urine, the result of the phenolsulphonphthalein test was 65 per cent and the blood urea 24 and 16 mg for each hundred cubic centimeters on different days. The patient was given the dietary regimen for nephrosis and advised to give up farm work for a sedentary occupation. In February, 1927, he wrote "Am feeling fine now. Have a lot of work and expect to do it all myself."

Comment—The chief point of interest in this case is that the association of high blood pressure and a high grade of albuminuria involved the differential diagnosis of glomerulonephritis and nephrosis.

CASE 4—A boy came to the Mayo Clinic on Aug. 17, 1926, for advice concerning his heart¹⁶⁴. Ten months previously, during the routine examination of candidates for the football team at his high school, "high blood pressure and leakage of the heart" were diagnosed, and he was placed on a rather strict regimen. He had felt so well that he wished to know if it were necessary to continue this life of restricted activity. Prior to October, 1925, besides doing his share of the farm work, he had been playing football, baseball and basketball with some local distinction. He had never noticed cyanosis, tinnitus, vertigo, headache, or pain, aching or weakness in the legs, but he had observed that his feet easily became cold. A harsh systolic murmur over the precordium, most intense in the second left interspace, was transmitted to the vessels of the neck. A diastolic murmur was not present in the aortic area, but one was audible along the upper part of the left border of the sternum, its character was not altered by change of position. Although there was no Corrigan or capillary pulse, the blood pressure sug-

¹⁶⁴ Blackford, L. M. Coarctation of the Aorta, Proc. Weekly Staff Meetings Mayo Clinic 1 103, 1926, 2 281, 1927.

gested aortic regurgitation. In attempting to elicit the "pistol-shot in the groin," it was observed that pulsation in the femoral artery was faint and less pronounced than in the inferior epigastric and superficial circumflex iliac arteries. The patient was urged to abandon his athletic career and to prepare himself to earn a living with a minimum of physical exertion. He wrote a year later that he was observing instructions and was in the best of health (fig 3).

CASE 5—In 1922, a boy who had suffered from many acute infectious diseases as a child was brought to the Mayo Clinic on account of poor physical endurance as demonstrated in a swimming test, he had no other symptoms. Because of high systolic blood pressure, he was limited in his activities and given a diet low in protein. He returned on Sept 1, 1926, for reexamination. Accentuation of the pulmonic second sound and a loud systolic murmur, greatest in the aortic area but also heard to the left of the sternum and in the neck, were observed.

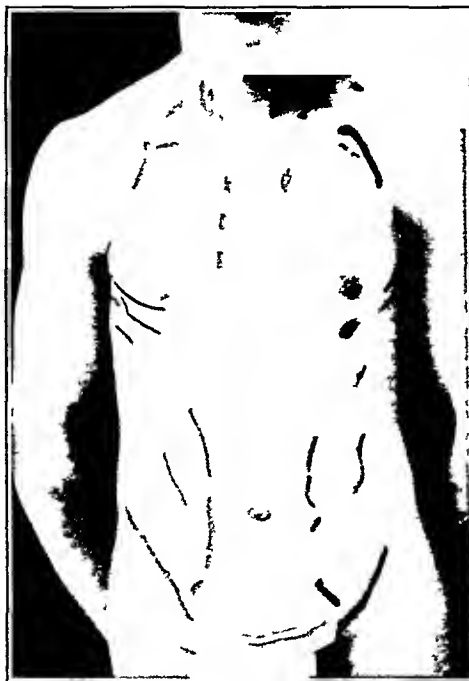


Figure 3



Figure 4

Fig 3 (case 4)—The muscular development of the subject is well shown. Attention is directed to the superior and inferior epigastric and musculophrenic arteries. In this and the following photographs, the collateral circulation was outlined by palpation on the body of the subject and checked by one or more other physicians.

Fig 4 (case 5)—Attention is directed to the prominence of the transverse cervical, intercostal, long thoracic, subscapular and circumflex iliac arteries.

The aortic second sound was roughened, but there was no diastolic murmur nor was any precordial thrill palpable. Coarctation of the aorta was first recognized at this time. On April 16, 1927, he was again examined. His mother said that her health had never been better than during the nine months preceding his birth. For about five years, his general health had been good, and he did not have subjective complaints. He was fairly well developed and well nourished, presenting a contrast to the sickly child of 1922, and he was proud of being able to make

his own living. The strictness of the diet had been gradually relaxed, but he was still observing instructions with regard to the avoidance of violent exercise. Dietary restrictions were removed, and three months later his color was better, but he was advised to continue the general regimen as regards exercise (fig. 4).

Comment on Cases 4 and 5—These two boys, aged 16 years, who were seen within a few days of each other were without symptoms. The first was an athlete of correspondingly good muscular development, the second had been forbidden to take part in athletics and was, therefore, not so strong. The lack of endurance in the latter at the age of 12 was probably more attributable to his various illnesses in the preceding six years than to the congenital lesion of the aorta.

CASE 6—A laborer, aged 46, sought relief at the Mayo Clinic on Dec. 30, 1926, for epigastric distress. He had led an active life, but had never noted dyspnea, palpitation, edema, headache, cold feet, nocturia or impairment of libido or potentia. At the time of a former abdominal operation, the surgeon had found the right rectus muscle unusually vascular. A harsh systolic murmur was heard at the aortic area, this was even more pronounced in the back, especially between the vertebral column and the upper part of the left scapula. Since the heart was not enlarged and the blood pressure almost normal, and since the patient was middle-aged and dependent on manual labor for his livelihood and denied cardiac symptoms entirely, it did not seem that an alteration in his mode of life was necessary.

CASE 7—A girl, aged 16, was brought to the Mayo Clinic on March 2, 1925, because of exophthalmic goiter. She had always been annoyed with cold feet, and had had momentary spells of difficulty in walking, but she had never experienced cardiac symptoms until 1922, when nervousness, weakness, palpitation, tachycardia, sweating and intolerance to heat caused her to consult a physician. The basal metabolic rate was found to be +25, the systolic blood pressure from 160 to 180 and the diastolic from 76 to 80, and a diagnosis of exophthalmic goiter was made, the symptoms subsided spontaneously. Two years later, the thyroid gland had enlarged perceptibly, and during the two months preceding admission to the hospital there had been violent recrudescence of the syndrome of goiter. Vomiting the previous week had been controlled by iodine, some improvement had occurred, but the patient was still critically ill. Stimulation, weakness, stare and sweating were all marked, and there was a loud bruit over each lobe of the thyroid gland. The first sound at the apex of the heart was snapping, and a systolic murmur was heard over the whole precordium, being transmitted to the axilla. The pulse was 110, the basal metabolic rate +62. After two more weeks of iodine treatment, the enlarged thyroid gland was resected, about one-fourth the normal amount of gland tissue being left on each side. Pathologic examination confirmed the diagnosis of exophthalmic goiter. Immediate convalescence from the operation was uneventful, and there was prompt and striking symptomatic relief with gain in weight.

After dismissal, however, the pulse remained rapid, and when compound solution of iodine was not being taken, the basal metabolic rate varied from +20 to +30. The patient returned Aug. 4, 1926. At this time, the left lobe of the thyroid was about twice normal size. During seven weeks of observation the symptoms of exophthalmic goiter could be controlled with iodine, but it became apparent that further resection of the gland would be necessary at some time, and the patient elected to have it done at once. Microscopic examination of the

specimen removed at the second operation was again reported as revealing hypertrophic parenchymatous thyroid gland. Sixteen days later, all evidence of exophthalmic goiter having subsided, the patient was examined again to determine the cause of the high blood pressure (systolic 206, diastolic 90), and coarctation of the aorta was diagnosed. She was dismissed with instructions to take ten drops of a compound solution of iodine daily for ten weeks. She returned on Jan 3, 1927, for reexamination, at this time, the basal metabolic rate was normal, and she felt well, but there was no change in the vascular condition.

Comment—The frank exophthalmic goiter masked the presence of coarctation in this case at first. The only other case in which thyroidectomy had been performed in a case diagnosed clinically or at necropsy as coarctation was one,⁹⁵ apparently of adenomatous goiter, in which operation was performed more than twenty years before death. Intermittent claudication has been noted in the history in one case previously diagnosed as coarctation of the aorta at the Mayo Clinic and in three so diagnosed elsewhere.

CASE 8—A woman, aged 22, came to the Mayo Clinic on July 6, 1927, complaining of nervousness and the loss of 10 pounds (4.5 Kg.) in the preceding six months. One sister had always been "nervous," and another had recently become so. Diffuse enlargement of the thyroid had been present for nine years. Three years before coming under observation she had been rejected on applying for work on account of "high blood pressure," and on another occasion on account of rapid pulse. Although strenuous exertion had always caused transient palpitation and tachycardia and she had lost blood through epistaxis many times up to 1925, she had considered herself in good health until the autumn of 1926, a few months after she was married. In September, she was shocked by the death of her father and about the same time she fell down five steps. A few days later, "things got black" before her eyes, she felt dizzy and her heart became rapid for a few minutes. A physician again found her blood pressure high, and prescribed a diet low in protein and salt. Following this, she became nervous and for several weeks apparently was on the borderline of a depressive psychosis. In January, 1927, there was a miscarriage of a six-months' fetus, and the symptoms became worse. The administration of compound solution of iodine (10 drops three times a day) was begun and continued for four months without improvement. The appetite had failed somewhat, and the feet were always cold. The thyroid gland was diffusely enlarged, and a bruit was heard all over it. At the apex of the heart, a systolic murmur was heard which became somewhat louder at the base and was transmitted into the thyroid gland and the infraclavicular fossa. This murmur was also heard distinctly in the left interscapular space. The basal metabolic rate was +20, but on further study the diagnosis of coarctation was made, subsequent rates were lower (fig. 5).

Comment—In the presence of a diffusely enlarged thyroid gland with bruit and thrill, an elevated basal metabolic rate, nervousness, tremor and some loss of weight, the presumable diagnosis would appear to be exophthalmic goiter. However, the patient's admittedly neurotic temperament and the various psychic shocks she had undergone in the previous year may explain some of the symptoms. The failing appetite,

cold feet, absence of exophthalmos and stare, the failure to improve under treatment with iodine and, above all, the general clinical impression, had caused the diagnosis of exophthalmic goiter to be discarded before the explanation of bruits and thrills over the thyroid gland was found in the diagnosis of coarctation

CASES OF COARCTATION DIAGNOSED AT NECROPSY IN THE MAYO CLINIC

CASE 9—A male infant was born on Sept 19, 1924. Respiration was retarded. Two days later, pallor and cyanosis with superficial respiration set in, and the next day he died. The heart was found slightly dilated and weighed 27 Gm. The

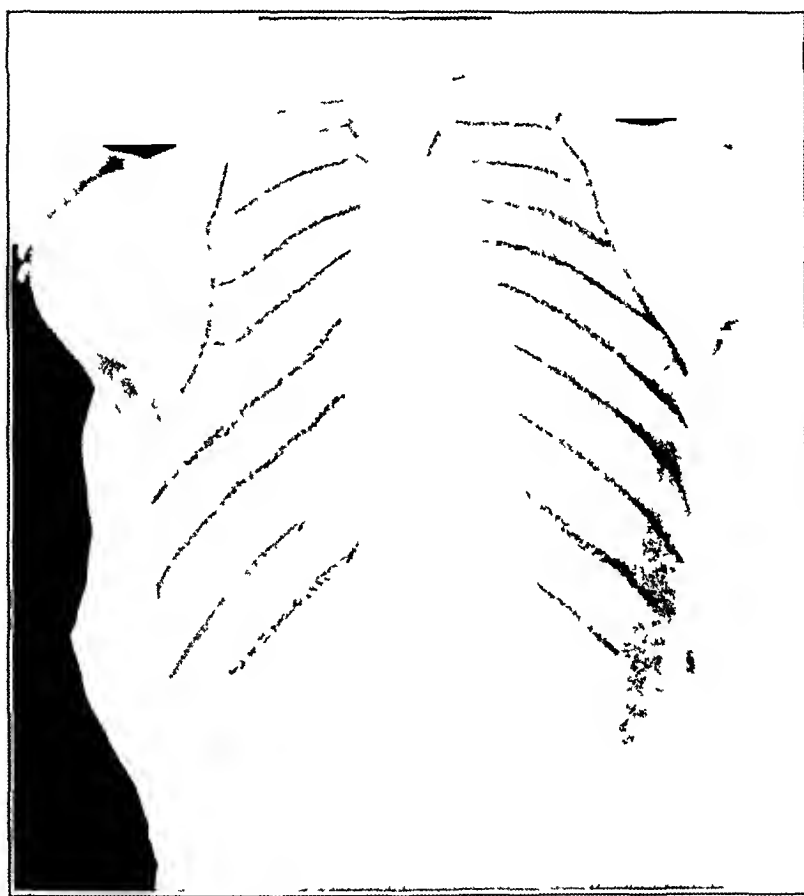


Fig 5 (case 8) —The anastomosis between the dorsal scapular and intercostal arteries. Blood is evidently flowing toward the aorta in the intercostals.

ductus arteriosus was widely patent, and the lumen of the aorta just proximal to its entrance was somewhat constricted. Other gross anomalies were not present.

CASE 10—A female infant, aged 3, was brought to the Mayo Clinic on June 2, 1923. She had been delivered with forceps, and artificial respiration had been necessary. She had always been delicate and extremely constipated. Five months previously, she had begun to have fainting spells, in these she would cry out, become pale and fall straight back. There was generalized edema, and the area of cardiac dulness was enormously increased. The action of the heart was regular. There was a definite blowing systolic murmur at the apex and a short blowing diastolic murmur along the sternum. The pulmonic second sound was

accentuated. A diagnosis of congenital cardiac disease was made, and six days later the patient died.

The heart occupied the whole width of the thoracic cavity, it weighed 215 Gm. The right auricle was greatly distended and the right ventricle was 12 cm in thickness as compared with 1 cm for the left ventricle. There was an inter-ventricular opening 1 cm in diameter. The ductus arteriosus readily admitted a fine probe. Just proximal to the opening of the ductus into the aorta there was marked constriction of the aorta by a valvelike ring, which, on approximation of the walls, almost closed the lumen. The arch of the aorta proximal to this was slightly narrow as compared with the thoracic aorta. Fetal lobulations of the spleen, incomplete rotation of the intestinal tract, horseshoe kidney, incomplete lobulation of the lung, ascites and anasarca were also noted.

CASE 11—A female infant with gross external anomalies was born on July 11, 1927. She suffered repeated convulsions, the respirations growing rapid and noisy, and died on the fifth day without ever having appeared cyanotic. The cardiovascular system was normal, except for marked constriction of the aorta just proximal to the mouth of the widely patent ductus arteriosus. The additional pathologic diagnosis was, "spina bifida (first four lumbar vertebrae) with meningomyelocele, extreme degree of internal hydrocephalus with hydromyelia, hemorrhages into the brain with terminal meningitis." This case strongly resembles one reported by Dreyfuss.⁹⁷

CASE 12—A man, aged 24, came to the Mayo Clinic on Feb 16, 1923, complaining of shortness of breath at night and pain in the right side of the neck on exertion. He had enjoyed good health except for occasional occipital headache until his discharge from the United States Navy in 1920. After this he noticed dyspnea with palpitation and tachycardia on mild exertion, and at night palpitation and later orthopnea, which he attributed to the fact that the "weakened artery" on the right side of the neck choked him when he was lying down. In the right supraclavicular fossa there was a tender pulsating mass, giving both systolic bruit and thrill. A diastolic murmur was heard in the aortic area. "Distention of the vessels of the back over both scapulas" was recorded, but pulsation in these vessels, in the abdominal aorta or in the arteries of the lower extremities was not noted. There was no cyanosis or edema. Moderate tenderness over the thoracic vertebrae was observed. A diagnosis of aneurysm of the right subclavian artery was made. Although the circulation in the affected arm was good after operation, the patient died from pneumonia on the tenth day.

The heart was diffusely hypertrophied, it weighed 450 Gm, and the thickness of the left ventricle was 1.5 cm as compared with 0.4 cm for the right ventricle. The aortic valve had only two leaflets. The aorta, which showed a minimal amount of arteriosclerosis, was completely obliterated just beyond the origin of the left subclavian at the insertion of a somewhat thickened ligamentum arteriosum. About 2 cm distal to this, the circumference of the aorta was 3.8 cm. The innominate artery measured 4.5 cm in circumference, and the branches of the right subclavian were greatly increased in size. From the costocervical trunk arose a tortuous artery 14 mm in circumference and 7 cm in length, which passed behind the esophagus to open into the aorta just above the origin of the third intercostal, its lower part was dilated to form an aneurysm about 2 cm in diameter. The brain and spinal cord were not examined (fig 6).

Comment—Although a vestige of the right dorsal aorta is not particularly rare, the presence of such an efficient trunk is exceedingly rare. In this instance it had evidently remained patent because it was needed.

as a blood channel, in other words, the obstruction in the left dorsal aorta must have occurred before the atrophy of the right dorsal aorta in the second half of the second month of embryonic life. This anomalous vessel must have been a rather efficient shunt for the aortic current, and perhaps due to it the blood pressure was found normal in the brachial artery, if so, it was of vast clinical significance as it removed a valuable clue to coarctation. In some other cases of bicuspid aortic valve, high pulse pressure has been found and attributed to relative insufficiency of the valve, however, in this and in the four cases of bicuspid aortic valve not associated with coarctation found at necropsy

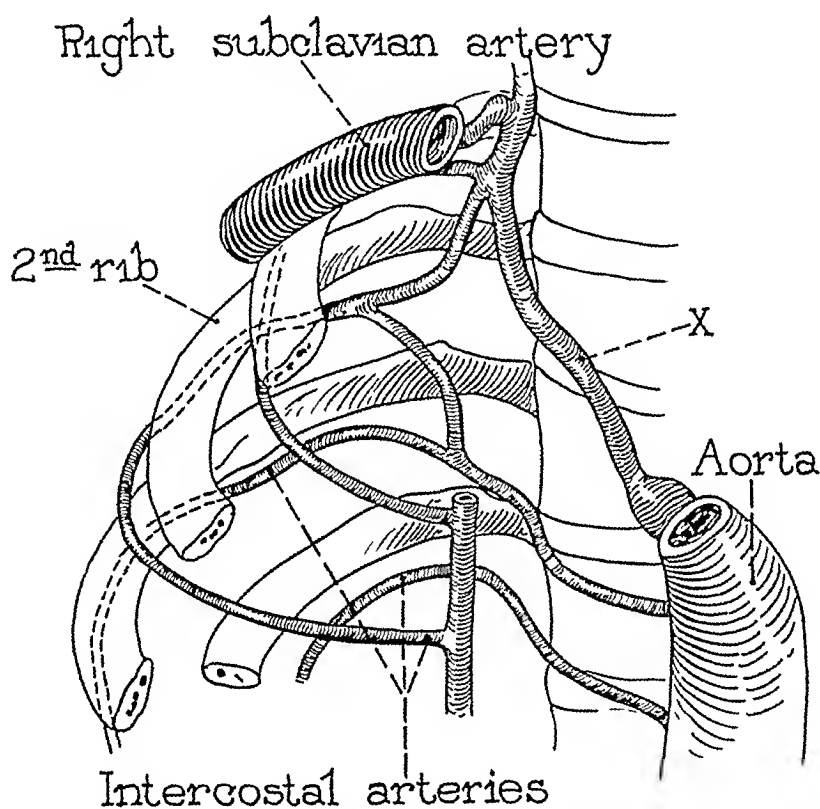


Fig 6—Persistent right dorsal aorta (X) in case 12 (diagrammatic)

at the Mayo Clinic, the blood pressure was essentially normal. In the only other case of aneurysm of the right subclavian artery associated with coarctation (clinical diagnosis),⁷⁵ death was due to rupture of the aneurysm, and it is probable that in the present case the patient would have died in the same way if operation had not been performed. The presence of a second aneurysm in this case is of interest. In view of the tenderness over the thoracic vertebrae and Haberer's report of the share of the anterior spinal artery in the collateral circulation in his case, it is to be regretted that the cord was not examined at necropsy.

There was nothing of significance in the family history of the adult patients in this series, nor any history of rheumatic fever. The results of the general examination of each patient were essentially negative,

TABLE 2—Summary of the Series of Cases in Adults from the Mayo Clinic

| Case | General Health | Size of Heart (Roentgenogram or Necropsy) | Collateral Circulation | Pulsation | | | Blood Pressure | | | | | | | | Electrocardiogram | |
|------|----------------|---|------------------------|------------------|-----------------|------------------|----------------|-----------|---------------|-----------|----------------|-----------|--------------|-----------|-------------------|----------|
| | | | | Retinal Arteries | Abdominal Aorta | Femoral Arteries | Right Brachial | | Left Brachial | | Right Femoral* | | Left Femoral | | | |
| | | | | | | | Systolic | Diastolic | Systolic | Diastolic | Systolic | Diastolic | Systolic | Diastolic | | |
| | | | | | | | | | | | | | | | | |
| 1 | Good | 1 | Good | Good | None | None | 161 | 86 | 126 | 110 | 90 | 80 | | | | |
| 2 | Fair | + | Not found | ? | None | None | 150 | 84 | | | 100 | | | | | Negative |
| 3 | Good | Normal | Good | ? | None | None | 200 | 110 | 180 | | 120 | | 135 | | | Negative |
| | | | | | | | 158 | 100 | | | | | | | | |
| 4 | Good | Normal | Good | Good | None | None | 164 | 53 | 162 | 62 | 80 | 60 | | | | Negative |
| 5 | Good | Normal | Good | | None | None | 180 | 100 | 165 | 100 | 108 | 60 | | | | Negative |
| | | | | | | | 160 | 76 | 156 | 82 | | | | | | |
| 6 | Good | Normal | Good | Absent | None | None | 158 | 96 | 154 | 98 | 102 | 80 | 106 | 88 | | Negative |
| 7 | Fair | Normal | Good | ? | None | None | 180 | 86 | 172 | 102 | 90 | 60 | | | | Negative |
| | | | | | | | 206 | 90 | | | | | | | | |
| | | | | | | | 176 | 104 | | | | | | | | |
| 8 | Fair | Normal | Good | Good | None | None | 168 | 94 | 164 | 90 | 102 | 88 | 98 | 84 | | Negative |
| 12 | Good | 2 | Present | | | | 128 | 88 | 122 | 90 | | | | | | |

* The first definite oscillation of the needle of the Tyco's sphygmomanometer (as the obliterating pressure decreased) was taken as the systolic blood pressure in readings on the thigh. In cases 4, 5, 6, 7 and 8, I made all readings except that on the thigh in case 7. In all cases the blood pressure was determined several times, usually by different observers and, except when made at long intervals, and the readings were in close agreement.

except the aneurysm in case 12. The Wasseimann reaction of the blood was negative in each case. The retinal arteries were tortuous in the cases examined.

Besides these cases of definite coarctation, four cases of slight constriction of the aorta with slight dilatation proximally were recently observed at the Mayo Clinic. They may be mentioned for two reasons: first, to illustrate varying grades of coarctation as found in the adult, for transition from a slight degree to atresia has previously been traced in infants, and, second, because the slight constriction was proximal to the insertion of the ligamentum arteriosum. It is worthy of note that in two of these cases the heart was distinctly small. But since the cardiovascular system had nothing to do with the previous health or the death of these four patients and the degree of constriction was slight, these cases will not be counted in the statistical study.

COMMENT

Bonnet's general observations have received increasing confirmation. There is no question that his infantile type is a result of prenatal maldevelopment. However, his deduction that the type overwhelmingly predominant in adults is the result of postnatal contraction of Botallian tissue in the wall of the aorta may be challenged. It has been shown that fibers from the ductus arteriosus do not normally extend appreciably into the wall of the aorta, and it has not been demonstrated that they ever do. As Virchow remarked seventy-five years ago, an anatomic hypothesis is a poor basis for a theory. The appearance of scarring and arteriosclerosis so often found near the insertion of the ligamentum arteriosum, both with and without coarctation, has been adequately explained by Meixner. Since the obliteration of the ductus is due to atrophy from lack of function, such a passive process could hardly effect contraction of the aorta, even if its fibers were present in the aorta. Moreover, as Bonnet was puzzled to observe, coarctation has been found associated with a patent ductus, in these cases, certainly this theory is inapplicable. These cases are equally potent arguments against the belief that obliterating endarteritis of the ductus is responsible for coarctation. The chief basis for this idea is the appearance of scarring in this region, which has already been explained.

The improbabilities of these two theories make it necessary only to consider the hypothesis that constriction or obliteration of the aorta at or distal to the mouth of the ductus arteriosus is of developmental origin. Congdon has shown that the segment of the definitive aorta represented by the left fourth branchial arch may be distal to the mouth of the ductus. If one continues to accept the older view in some cases, the site of coarctation is that segment of the aorta represented by the fourth arch.

in all cases. This arch when proximal to the ductus undoubtedly may become occluded or fail to develop normally from some inherent defect or other cause, it is then reasonable to assume that this embryonic structure when distal to the ductus may also be subject to maldevelopment. If this occurs in utero, the collateral circulation may be mapped out and developed at the same period and in the same way as other definitive arteries, and thus cause little disturbance. Since no additional strain would be placed on the right ventricle under such circumstances, it is not surprising that the interventricular septum should develop normally, as it usually does in the adult type.

Of the positive arguments that coarctation of this type is the result of defective arterial primordia, one of the most important is the common association of other developmental defects of the vascular system. Rupture of the aorta without aneurysm and aneurysm of the aorta or of cerebral or other arteries in nonsyphilitic young persons so often associated with coarctation are probably a result of imperfect development. Bicuspid aortic valve, one of the rare anomalies, is found in about 25 per cent of the cases in adults, and general hypoplasia of the aorta, which seems to be half as common as coarctation, is associated in about 10 per cent. Other examples of serious maldevelopment are not infrequent. Thus the presence of associated arterial or valvular anomalies is additional support for the embryonic origin of coarctation in the adult. Further, the case from the Mayo Clinic and the several reviewed in the literature in which the constriction was proximal to or involved the origin of the left subclavian and, above all, the new case which I have reported in which the right dorsal aorta was persistent, must all have dated from the second month of embryonic life.

In the series of fifty-seven cases in adults which I have reviewed definite syphilitic changes in the aorta were found in only two, in a number it is expressly stated that there was no evidence of syphilis. These figures are in accord with those of earlier authors. As evidence of the disease is infrequent in such cases, and since there is little to show that syphilis can obliterate a large artery, the burden of proof that syphilis is of etiologic significance in coarctation rests on supporters of the theory that it is.

However, if the challenge to Bonnet's division with regard to pathogenesis is made good, this classification remains of clinical value as of the 323 cases of coarctation verified at necropsy, death occurred during the first year in 125 and during the first decade in 142. Of the 173 persons who survived this period and whose ages are given, 112 died between the ages of 16 and 40 inclusive, forty-six of these, in the third decade.

In three cases, collateral vessels were looked for but not found during life, the diagnosis in such cases would be strongly suggested by the marked difference in blood pressure in the brachial and femoral arteries. The clinical reports of cases studied that came to necropsy mentioned the presence of collateral vessels twenty-eight times, in these, atresia was found twelve times and extreme stenosis, sixteen, of the eighteen definitely diagnosed in life, atresia was present in eight cases and extreme stenosis in ten. Postmortem protocols show that collateral arteries were often overlooked in life, indeed one case²⁴ was diagnosed by the pathologist from external examination. The detection of pulsating vessels along the vertebral border of the scapulas and elsewhere over the thorax is therefore presumptive evidence of marked narrowing or occlusion of the aorta at the beginning of the descending part, although extreme stenosis can be distinguished from atresia only at necropsy. Visible pulsation of the arteries of the neck, a prolonged systolic murmur in the interscapular space or high pulse pressure should suggest a search for these. Systolic blood pressure exceeding 150 was found in thirty-three of thirty-five cases in which the systolic pressure was given and a pulse pressure exceeding 70 in twenty-two of twenty-seven cases in which it was given. This high pulse pressure, together with the bruit and thrill over the thyroid gland, emphasize, as Louga pointed out forty years ago, that these data are insufficient for the diagnosis of exophthalmic goiter, which they are likely to suggest. Collateral circulation due to intra-thoracic tumor is so rare that it can seldom confuse the picture. A total of eight cases has been reported in which no evidence of collateral circulation was found at necropsy.

In some cases, such as Horde's, coarctation is not intrinsically the most important factor in the death of the patient. In this instance, the constriction was mild, and the rupture of the aorta was evidently due to defective development at the site of the rupture and was not secondary to the coarctation. At least thirty-five cases already referred to belong in this group. There is another group in which the narrowing of the trunk is not marked and is of merely pathologic interest. The majority of such cases cannot be diagnosed clinically, and it is not important that they should be.

The circulation to the lower part of the body is sometimes functionally perfect in cases of extreme coarctation, as proved by the women who have borne several children, and it may be only an incidental post-mortem observation, as is proved by the men who have led strenuous lives as soldiers, sailors or laborers. However, it is the duty of the physician to recognize, whenever possible, coarctation without symptoms, for after symptoms of cardiac failure appear it is too late to advise the patient that he may have a better chance of avoiding cardiac failure or

rupture of a vital vessel. These are real dangers in cases of coarctation, for 147 persons with coarctation, verified at necropsy in a series of 196 adults, died from causes more or less directly related to the stenosis. Sixty-eight died from gradual cardiac failure, sixteen died suddenly from the same cause. Spontaneous rupture of the aorta caused the death of thirty-eight persons, and cerebral hemorrhage of twenty-five more. It has been appreciated for some time that there is a peculiar relationship between congenital cardiac disease and subacute bacterial endocarditis, in six of the sixty cases in adults reviewed or reported in this paper, death occurred in this way, as well as in a number in the earlier reviews. Endocarditis was present in another instance in this series, and bacterial aortitis was the cause of death through rupture of the aorta in two other cases.

As 76 of the 180 subjects aged more than 5 years, whose age is available, died during the years between 16 and 30 inclusive, and since 36 others died during the next decade, the responsibility of the physician who is consulted by a young person with this anomaly is great. When of clinical significance, coarctation can usually, if not always be diagnosed. The possibility of detecting it should cause the physician who makes routine examinations of large numbers of young persons to bear it ever in mind. It may be emphasized again that many of the victims of this condition were young athletes who died during or shortly after exercise, and who might have achieved their normal life expectancy if all unusual strain on the cardiovascular system had been removed. The possibility of the presence of coarctation is an additional reason for the general examination of every one contemplating violent physical exercise, irrespective of his previous health.

When the diagnosis is made, not only should a regimen of limited physical activity be prescribed, but all possible foci of infection should be removed on account of the danger of bacterial endocarditis or aortitis. There is no apparent indication for dietary restriction.

SUMMARY

Narrowing or obliteration of the aorta in the region of the mouth of the ductus arteriosus or its vestige is believed to be due to absence, atrophy or imperfect development of the left fourth branchial arch. Syphilis is not an etiologic factor.

The division into the infantile type, in which the constriction is proximal to the ductus, and the adult type, in which it is at or just distal to it, though not precise, is convenient morphologically and clinically.

Coarctation has been found in 127 necropsies on infants and young children. The clinical diagnosis in such cases is of little or no actual

importance, because coarctation of the infantile type is rapidly fatal, or, if of the adult type, hardly a factor in causing death

Coarctation has been found in at least 196 necropsies on older persons. More than 40 per cent of these were from 16 to 30 years of age, and more than 70 per cent died from cardiovascular causes. In addition, coarctation in thirty-five cases was overshadowed by other cardiovascular defects of developmental origin.

Coarctation has been diagnosed clinically in seventy-eight cases and corroborated at necropsy in twenty-one of these. The diagnosis is often suggested by an unusually high pulse pressure or by a loud systolic murmur in the left interscapular space, and confirmed by the presence of pulsating superficial arteries over the thorax and the diminution or absence of pulsation in the abdominal aorta and femoral arteries.

Coarctation once diagnosed indicates the removal of possible foci of infection and, especially if the patient is a robust, athletic young man, a regimen of limited physical activity.

CHONDROMA OF THE SPINE ASSOCIATED WITH A TRANSVERSE MYELITIS

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Cartilaginous tumors are frequently encountered as small outgrowths from preexisting cartilaginous structures (ecchondroses) and as larger growths originating in cartilage or other tissues (enchondromas). Usually the larger neoplasms are readily diagnosed because of the tendency to cause visible deformity or symptoms of obstruction. Of all the bony structures the spine is singularly free from obstructive tumors of this type. It is because of the rare occurrence of this condition and the unusual pathologic aspects that the following case is reported.

REPORT OF A CASE

Clinical History—A negro, a laborer aged 23 in September, 1918 was confined to the hospital for two weeks with an attack of influenza. In December, 1918, he complained of frequent 'drawing and sharp shooting pains in the lower part of the abdomen and both lower extremities, accompanied and followed by marked weakness of the legs.

In January, 1919 he suffered an attack of mumps, after which weakness of the legs became more pronounced. He experienced sharp pains in the lower part of the back. Within a period of seven days he gradually lost power of voluntary movement in both lower extremities. In the following eleven months, he received intravenous treatment for syphilis (details not available), without improvement.

In July 1920 he entered the U S Public Health Service Hospital, Cape May N J. Clinical notes at this institution indicated the presence of a paraplegia, urinary and fecal incontinence, nocturia, pain in the lower spinal region and impaired sensation over both lower extremities.

In September, 1920 he was admitted to the U S Public Health Service Hospital 38 New York. The following is a report of a physical examination made at that time.

Physical Examination—A young negro was lying quietly in bed. The knees were semiflexed and the feet extended. Occasional jerking movements of the lower extremities were noted. Decubitus ulcers approximately 3 by 5 cm and 2 by 4 cm. were seen over both buttocks exposing the muscle tissue. There was no evident enlargement of the heart. A presystolic murmur was present and confined to the apical region. In the upper thoracic region of the spine there was a slight dorsal irregularity of contour which was markedly tender to pressure. The cervical, axillary and inguinal nodes were palpable.

There was a temporal pallor of the right optic disk. The pupils were irregular, unequal (the left being miotic) and sluggish in reaction to light. Flaccid paraplegia involved the muscles of the lower part of the trunk, causing difficulty in maintaining an upright posture even while sitting. There were clonic tremors of the legs particularly of the left one, caused by any attempt at voluntary movement of the upper part of the body or passive motion of the leg or foot. These movements

ceased on deep pressure. The muscles of the legs were flabby. The faradic response of the muscles of the right leg and of the thigh were 0.1 microfarad, left leg, 0.05 microfarad and left thigh, 0.01 microfarad.

Below a level corresponding with the third rib, tactile pain and thermic sensation were abolished. In this area, the patient could not discriminate between two points, and the posture sense of the legs was lost. The vibratory sense tested by means of the tuning fork was interpreted as pain. Just above this analgesic and anesthetic area was a zone of hyperesthesia and hyperalgesia.

All reflexes were abolished in both lower extremities. There was no Babinski sign or true ankle clonus. The cremasteric and abdominal reflexes were absent. Involuntary micturition and defecation were present.

Laboratory Data—The Wassermann reaction was negative on five occasions. One blood culture was negative a few days before death, having been taken during a septic period. Three examinations of the spinal fluid were made. The following report is representative: amount, approximately 25 cc, color, xanthochromic, turbidity, none, cytologic, 40 lymphocytes per cubic millimeter, globulin, present,



Fig 1—Lateral view (left side) of spinal column showing posterior nerve root and sympathetic trunk emerging from tumor mass.

sugar, none, colloidal gold test, invalidated by the presence of dissolved hemoglobin, Wassermann reaction, negative on three occasions, and guinea-pig inoculation, negative for tuberculosis at the end of six weeks.

Roentgenographic Studies—Roentgenographic studies of the chest revealed a mass, somewhat triangular in outline, approximately 5 cm in length and 3 cm in width, occupying the region of the second rib on the left side. The mass extended to the median line and invaded the bodies of the first and second dorsal vertebrae. Examination of the upper dorsal to the lower sacral spine by means of the Dandy technic revealed an ovoid, irregularly outlined mass extending from the articulation of the third left rib, close to the vertebral junction, obliterating these structures. The mass was distinctly calcareous and probably not malignant.

Clinical Course—The clinical course was marked by a gradual development of sepsis due to the progressive extension of decubitus ulcers on the buttocks. Death occurred on Oct 15, 1920, approximately two years after onset of the symptoms.

Gross Pathology—The specimen submitted for examination consisted of a resected portion of the spinal column, including the spinous processes and bodies of the last two cervical and upper three dorsal vertebrae with about 5 cm of rib attached to three of the latter. Extending anteriorly and to the left, involving the spinous processes and posterior aspect of the bodies of the first and second dorsal vertebrae and adjacent portions of the ribs on the left side was a hard, grayish, partly translucent, smooth, irregularly lobulated tumor. The lobules varied in size from 2 to 25 mm. A posterior nerve root and what was apparently a trunk of the sympathetic nerve were seen to emerge, somewhat distorted, between and firmly embedded in lobules of the tumor. On removing the laminae of the involved and adjacent vertebrae, the mass was seen to project directly forward into the spinal canal for a distance of from 15 to 17 mm over a vertical extent of 40 mm. The posterior nerve roots were stretched taut, and the cord itself, covered by its membranes, was compressed to a mere ribbon. A small amount of old clotted blood was seen in two small triangular spaces just above and below that portion of the tumor which projects into the canal. Many small varicosities were to be seen on the posterior surface of the vertebral bodies for



Fig 2—Lateral view (right side) of spinal column, with laminae removed, showing the tumor projecting forward into the spinal canal and compressing the cord (Arrows point to cord)

a short distance above and below this region. Some calcified portions and small round areas of cystic degeneration were evident in the larger lobules. Typical golden yellow spinal fluid was present in the canal below the tumor mass. By careful dissection, a perichondrium could be demonstrated encapsulating the tumor, and septums of connective tissue separated the lobules. The cut section was typically bluish and translucent.

Microscopic Pathology—Sections taken from one of the larger lobules showed a mixed hyaline and fibrocartilaginous structure. The cells appeared to be more numerous than in normal cartilage. They occurred singly or in groups of from two to six lying in clear elongated cell spaces. They appeared to be almost round, except where many were grouped together, in which case the opposing surfaces were flattened. Variations in size, irregularity and distribution and arrangement indicate an abnormal cartilaginous structure. Thin sections do not take a deep stain with hematoxylin-eosin.

EPICRISIS

Clinical Aspects—The etiology of chondroma is not always clear. The majority of these tumors occur early in life, about the time of puberty. Most chondromas occurring in connection with bone begin before ossification of the epiphysis has occurred, at a period in which the bone is actively growing and vascular. Multiple chondromas of the spine are hereditary and congenital. The hereditary predisposition is

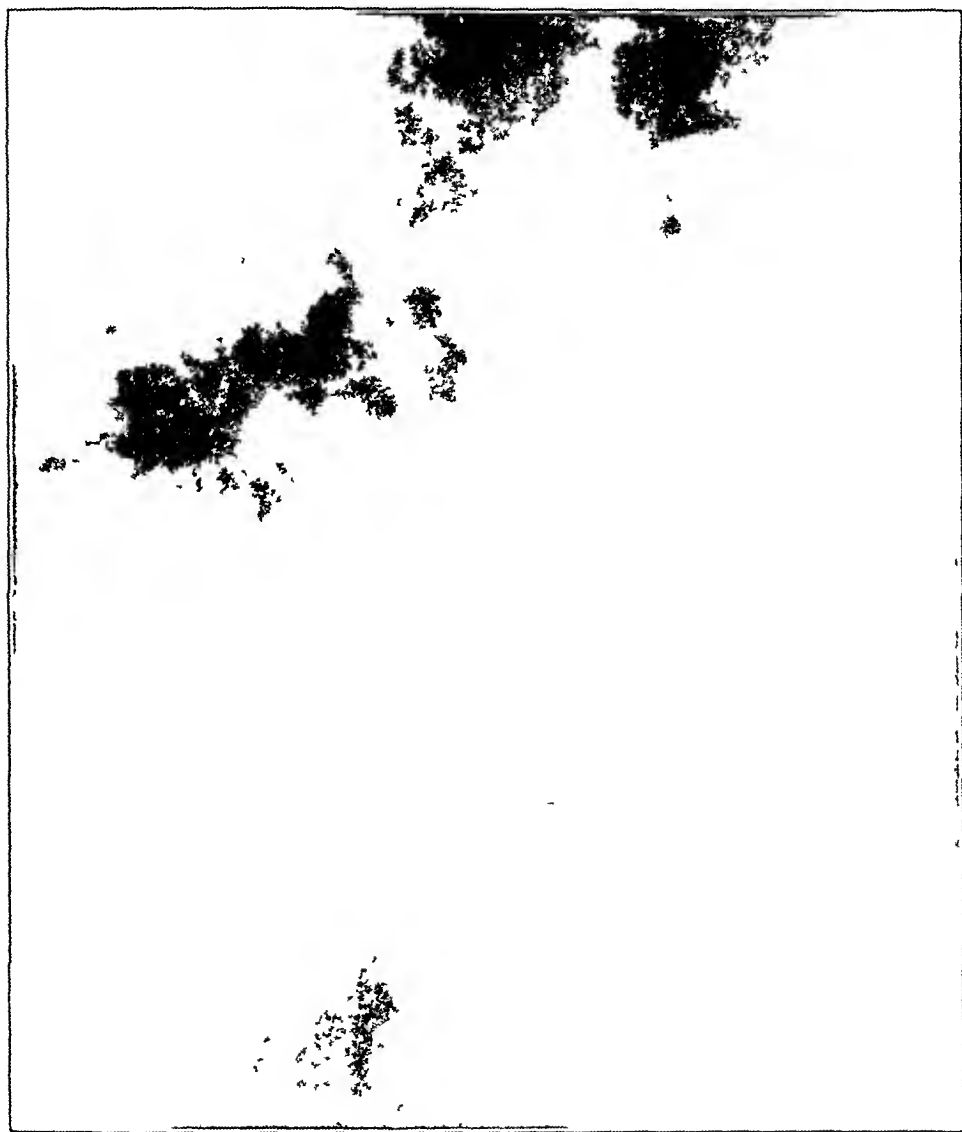


Fig 3—Roentgenographic appearance of tumor mass (anteroposterior view). Note the diffuse distribution of calcareous deposits. Positive print.

stressed by Weber,¹ who observed this type of tumor in several members and three generations of the same family. Herxheimer² attributed

1 Weber, C. O. *Die Knochengeschwulste*, Amtl. Ber. u. d. Versamml. deutsch. Naturf. u. Aerzte, Göttingen 31.164, 1860.

2 Herxheimer, G. *Grundlagen der pathologischen Anatomie*, ed. 2 and 3, p. 102.

many of these chondromas to heterotopic rests, while Virchow³ pointed out that the frequent occurrence of chondroma in young people is caused by displaced cartilaginous islands cut off during endochondral ossification. Borst⁴ described isolated islands of cartilage in rachitic bone, and Muller⁵ found similar deposits in the periosteum of the ribs. The theory of heterotopic rests is probably not applicable to all chondromas, as periosteum and endosteum normally form cartilage readily. Trauma and inflammation are factors in some cases. In this

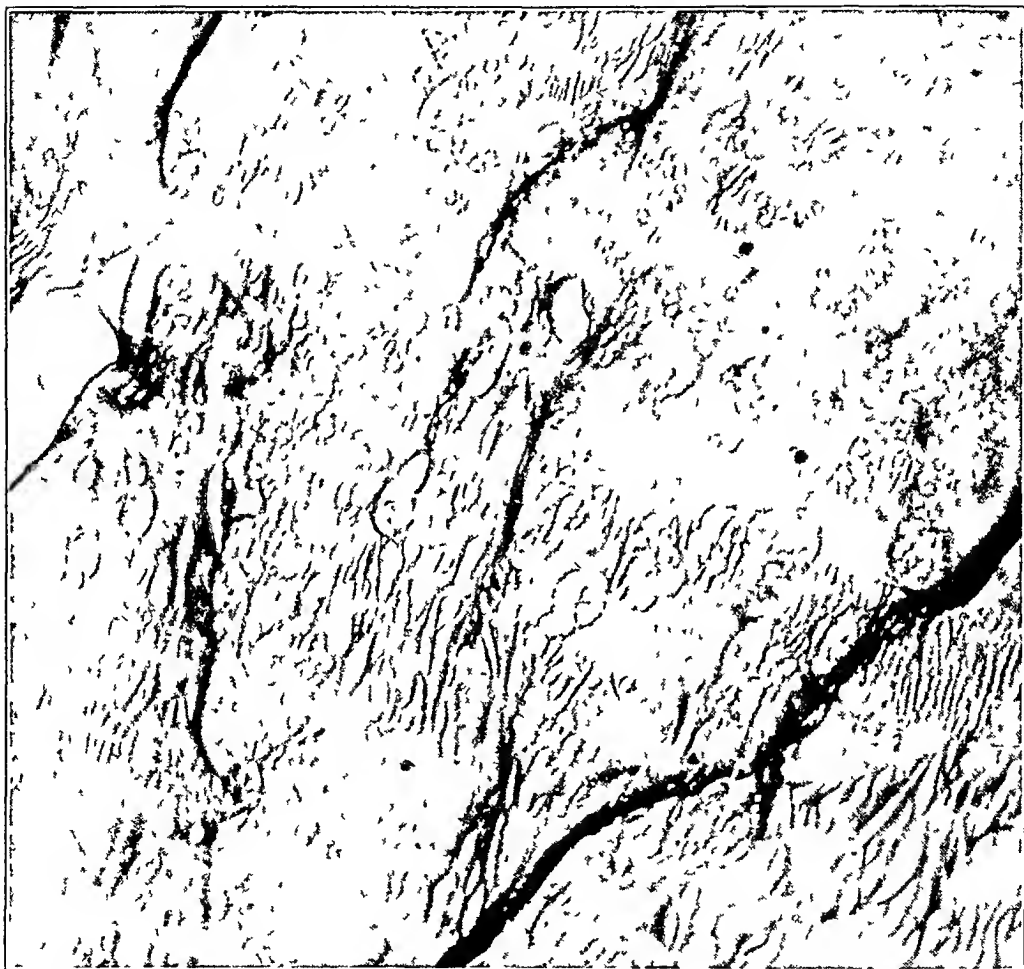


Fig 4—A section taken from the tumor. Note the variation in the size and shape of the cells as well as their irregular distribution and arrangement.

patient the onset of symptoms following influenza and mumps appeared to be significant. A possible infection of the intervertebral disks followed by marked overproduction of cartilage—a process so common in the negro—might account for the formation of a chondroma.

3 Virchow, R. *Deutsche Klin* 9 90, 1864

4 Borst, M. *Pathologische Histologie* 2 342, 1926

5 Muller, E. *Beitr z path Anat u z allg Pathol*, vol 57, pp 232-281

Transverse lesions of the spinal cord as a result of caries or tumor of the spine are rarely complete. In total transverse lesions, there is complete sensory and motor paralysis and complete loss of tendon reflexes in parts supplied below the segmental level of the injury. The muscular paralysis is of the flaccid type, with rapid wasting and loss of faradic excitability. The development of paraplegia is gradual and usually precedes the loss of sensation. The early symptoms are weakness of the lower limbs or peculiar sensations of numbness, tingling or pins and needles. It is interesting to note that paraplegia caused by pressure on the spinal cord may persist for as long as a year and yet recovery be complete after removal of the tumor. The zone of hyperesthesia described in this case is not always present. There is loss of sphincteric control (bladder and rectum). Certain skin reflexes may occasionally persist (e. g., plantar reflex with dorsal flexion of the great toe).

*Physiologic Aspects*⁶—Based on present knowledge of the functions of the tracts, the location and extent of neuro-anatomic injury in the case presented may be stated briefly as follows: (1) Sensory pathways: funiculus gracilis, cuneatus, cerebellospinalis, anterolateralis superficialis, cerebrospinalis lateralis, lateralis proprius, which constitute long ascending tracts in the posterior and lateral funiculi of the cord. Their function is to convey muscle sense. Short association tracts of the lateral and anterior funiculi, which are probably the pathways for touch, pain and temperature. (2) Motor pathways: funiculus cerebrospinalis lateralis et anterior, intermediolateralis, which control voluntary movement. (3) Reflex pathways. In this connection, mention may be made of the physiologic centers for defecation and bladder control. These probably lie in the lumbar cord, both acts being in the nature of involuntary reflexes.

In explanation of the length of time the patient survived an almost total deprivation of most of the spinal cord, it is interesting to recall the experiments of Goltz and Ewald.⁷ In steps, they removed the entire cord except the cervical and a small part of the upper thoracic regions, thus simulating the lesion in my patient. With great after-care they succeeded in keeping their animals alive for a long period, the digestive, circulatory and excretory organs performing in a normal manner. This indicates that the visceral organs are more independent of direct control by the nervous system. The adaptability of the cordless portion of the animal and the power to preserve a constant body temperature were less than normal and the susceptibility to inflammatory disturbance greatly increased. The gradual loss of functioning cord tissues by

6 Howell, W. H. Text Book of Physiology, Philadelphia, W. B. Saunders Company, 1911, 155-156, 168-182, 244-250, 722-723 and 843-844.

7 Goltz and Ewald. Arch. f. d. ges. Physiol. 63: 362, 1896.

pressure of the tumor probably afforded an opportunity for the patient, as in the case of Goltz' animals, to adapt himself to a modified mechanism of nervous control. Clinical reports indicate recovery of function after removal of tumors which have compressed the spinal cord for as long as a year.

*Histologic Aspects*⁸—Cartilage is a tissue of mesodermal origin. The cartilage cell seems to be an end-product of the connective tissue cell which has acquired the special function of producing fibroglia, collagen or elastic fibrils and the ability to secrete a dense homogeneous intercellular substance known as chondromucin⁹. In the process of transformation, the fibroblast becomes spherical or flattened and appears to lose its fibroglia fibrils. At first the cartilage is wholly cellular. As the intercellular substance increases, lighter and denser areas are formed about individual cells or groups of cells giving the appearance of hyaline capsules. Hyaline, fibrous or elastic cartilage results depending on the nature and quantity of the intercellular matrix. New cartilage¹⁰ is always the product of cells at the periphery which are more like fibroblasts in appearance. The latter cells form a fibrillar connective covering, the perichondrium, which blends almost imperceptibly with the superficial layers of cartilage. In a similar manner, cartilage cells may arise from fibroblasts composing periosteum. The cartilage cell possesses ameboid properties and is prone to metaplastic change¹¹.

Pathologic Aspects—Cartilaginous growths occurring as simple hyperplasias of preexisting cartilage are usually multiple and small, springing from the edges of the articular cartilage and passing through the capsular ligament. This type of hyperplasia is generally referred to as an ecchondrosis and is probably the result of chronic irritation. The ribs, larynx, intervertebral disks and the area about joints are rather common sites. The general structure is that of normal hyaline or fibrocartilage, being surrounded by a normal perichondrium which, according to von Rindfleisch,¹² is the point of origin.

True progressive neoplasms composed of cartilage occur in the same regions as ecchondroses, but also in soft tissues and internal organs. This type of tumor is known as chondroma or enchondroma and is

8 Bailey, F. R. Text Book of Histology, New York, William Wood & Company, 1910, p. 90.

9 Mallory, F. B. The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1923, p. 291.

10 McFarland, J. Surgical Pathology, Philadelphia, P. Blakiston's Son & Company, 1924, p. 243.

11 MacCallum, W. B. Text Book of Pathology, Philadelphia, W. B. Saunders Company, 1924, p. 950.

12 Rindfleisch, E. Lehrbuch der pathologische Gewebelehre, Leipzig, 1886, p. 155.

often probably the sequel of a simple hyperplasia. It is found most frequently on the metacarpal bones and phalanges, usually being multiple and at the epiphyseal line. The femur, ribs, scapulae and pelvis are not infrequent sites. The typical chondroma is usually seen as a dense rounded, nodular or lobulated tumor, appearing translucent, pale bluish or opalescent white on section. The gross appearance depends largely on the age, rapidity of growth, state of nutrition and type of cartilage making up the tumor. The size may vary from a single small tumor weighing a few grams to a large lobulated mass of several kilograms (pelvis). There is an encapsulating dense layer of connective tissue made up partly of perichondrium, which is the source of growth and partly of displaced and compressed connective tissue derived from the invaded area. The lobulation is outlined by fibrous vascularized septums which spring from the capsule and, according to Ewing, represent growths from multiple centers. Nutrition is maintained by a system of lymph spaces from the periphery of the lobule (von Rindfleisch and Boist¹³). Chondromas are usually broadly connected with bone or cartilage. They may be partly embedded in the marrow cavity, the superficial portion breaking through the cortex. The external or periosteal chondroma may, by pressure atrophy, cause the formation of a fossa in the surface of the bone. The centrally situated chondromas are usually multiple. Some cases have been reported in which nearly every bone was involved.

Secondary changes are common. Calcification or ossification, mucinous degeneration with cyst formation, are the usual changes encountered. The tendency to calcification or ossification appears to be enhanced by the presence of many vascularized septums of the connective tissue. Virchow¹⁴ and von Recklinghausen¹⁵ believe that the highly vascularized areas found about many chondromas play an important part in the development of the tumor. Blood vessels may grow into the cartilage as in normal endochondral ossification and convert it into bone. Ossification is most common in tumors springing from the junction of epiphysis and shaft of a long bone. Cysts filled with mucinous, serous or fatty material may be formed. Large tumors which reach the skin may stretch it and cause ulceration. Most chondromas occurring in connection with bone begin before ossification.

13 Von Rindfleisch and Boist, in Ewing, J. *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1922, pp. 185 and 189. Delafeld, F., and Prudden, T. M. *Text Book of Pathology*, New York, William Wood & Company, 1925, p. 402.

14 Virchow, R. *Cellular Pathology*, trans. by Chance, New York, R. M. De Witt, 1860, p. 445.

15 Von Recklinghausen. Multiple Enchondrom der Knochen in Verbindung mit multiplen phlebogenen cavernösen Angiomen der bedeckenden Weichtheile, *Virchows Arch. f. path. Anat.* **118** 4, 1889.

of the epiphysis has occurred, at a period when the bone is actively growing and vascular

The microscopic processes in chondroma are largely the same as those seen in the structure of normal cartilage. Ernst¹⁶ described all of the variations in great detail. Any or all three types of cartilage may be found in one tumor, but hyaline cartilage is most frequently seen. Ranvier¹⁷ divided chondromas into four groups: (1) single lobe of hyaline cartilage, (2) several lobules of hyaline separated by fibrocartilage, (3) fetal cartilage, and (4) cartilage with stellate cells. The general appearance of the cells resembles that of normal cartilage, except that they vary greatly in size and shape and in the orderly grouping of cells lying in lacunae with opposed surfaces flattened. The cells may contain vacuoles ("physaliden" of Virchow), mucin or calcium granules. Glycogen and fat granules are commonly present. The size and shape may vary from large polymorphous cells to stellate rounded or small spindle-shaped forms, the latter lying near the periphery and constituting the actively growing portion of the tumor. This region adjoins the vascularized stroma which, by means of its septums separates and brings nutriment to the individual lobules. As growth proceeds, this stroma is stretched, and the cells farthest removed from it are apt to undergo mucoid degeneration, calcification or necrosis.

The matrix of a chondroma is usually hyaline, but may be fibrous or elastic. Calcium deposits first affect the matrix and appear as deeply basic staining granules made up of phosphate and carbonate. Ribbert is of the opinion that the matrix is a product deposited under cellular influence. The younger portion of the tumor is apt to be more cellular and contain less matrix. The cells may or may not possess a capsule.¹⁸ According to Aschoff,¹⁹ the young cells generally are devoid of a capsule. When present, the capsule shows a fibrillated structure.

SUMMARY

A case of chondroma of the spine associated with transverse myelitis is described. The slow development and benign character of the tumor suggest that even delayed surgical measures may be consistent with cure. Persistent arsenical treatment of a negro with symptoms pointing to a lesion of the spinal cord should be avoided without preliminary roentgenographic studies of the spine.

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16 Ernst, P. Ueber den feineren Bau der Knorpelgeschwulste, *Beitr. z. Path. Anat.* **38** 67, 1905.

17 Ranvier. Contribution a l'etude de la structure et du developpement des tumeurs cartilagineuses, *Bull. de la Soc. Anat. de Paris* **40** 534, 1865.

18 Zeigler, E. General Pathology, trans. by Symmers, New York, William Wood & Company, 1921, p. 298.

19 Aschoff, L. Pathologische Anatomie, Jena, G. Fischer, 1913, p. 690.

THE RECIPROCAL RHYTHM

REPORT OF A CASE IN WHICH AURICULAR TACHYCARDIA WITH
PARTIAL A-V DISSOCIATION AND ATRIOVENTRICULAR BRADY-
CARDIA, WITH RECIPROCATING RHYTHM, WERE PRESENT *

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In 1913, Mines¹ described a curious rhythm occurring in the heart of the ray and of the frog after electrical stimulation. This rhythm continued for a considerable period after a single shock, and could be interrupted and abolished by a second stimulus applied either to auricle or ventricle. The mechanism consisted of a sequence of auricular and ventricular contractions, equally spaced and apparently due to an impulse originating in either chamber and transmitted over the usual conduction path to the other, returning again to the first over the same pathway and repeating this process indefinitely. Mines assumed that part of the conduction pathway must have been refractory during the passage of the impulse in one direction, with recovery and transmission in the opposite direction when the second chamber contracted and while the initially active fibers were refractory.

A similar mechanism has not been observed in the heart of mammalia, either experimentally or accidentally. However, in 1924, Drury² recognized the similarity between the "reciprocating rhythm" of Mines and a type of bigeminy which occurs during atrioventricular rhythm in man. In this condition an auricular beat falls near the end of systole of the first ventricular beat of the couplet.

This arrhythmia was first described by Wenckebach³ in 1906, from polygrams taken of a boy, aged 12 years, with compensated rheumatic heart disease. He interpreted these curves as showing dissociation of the auricles, the left auricle maintaining a steady rhythm in the ventricles the right auricle beating more slowly. When the right auricle contracted after the refractory period of the ventricles had ended they responded to it, giving the appearance of an interpolated extrasystole in the tracing.

* From the Department of Medicine, Stanford University School of Medicine

1 Mines, G R. On Dynamic Equilibrium in the Heart. Reciprocating Rhythm, *J Physiol* 46:376, 1913

2 Drury, A N. Paroxysmal Tachycardia of A-V Nodal Origin Exhibiting Retrograde Heart-Block and Reciprocal Rhythm, *Heart* 9:405 1924

3 Wenckebach, K F. Beitrage zur Kenntnis der menschlichen Herztätigkeit. Ueber Dissoziation der Tätigkeit beider Vorkammern, *Arch f Anat u Physiol, Physiol Abteil*, p 349 and Taf IV, p 561, 1905

of the radial pulse. As polygraphic curves illustrative of this disorder are rare, I have reproduced one of Wenckebach's curves (fig 1)

The electrocardiogram of this type of bigeminy was described by Gallavardin⁴ in 1914, in two patients who had nodal rhythm as a result of the administration of atropine or of ocular pressure. Gallavardin regarded the auricular and ventricular complex which composed the second half of the couple as a normal supraventricular beat. White,⁵ who reported a similar case in 1915, described the second ventricular beat as due to a return to the ventricle of the impulse which had reached the auricle by retrograde conduction. He reported three later cases,⁶ Gallavardin reported another,⁷ and Wilson⁸ observed the same phenomenon in a patient in whom nodal rhythm was a result of atropine medication. Wilson explained the coupling as due to ventricular response to an auricular beat falling between the R and T wave. Bishop⁹ reported a

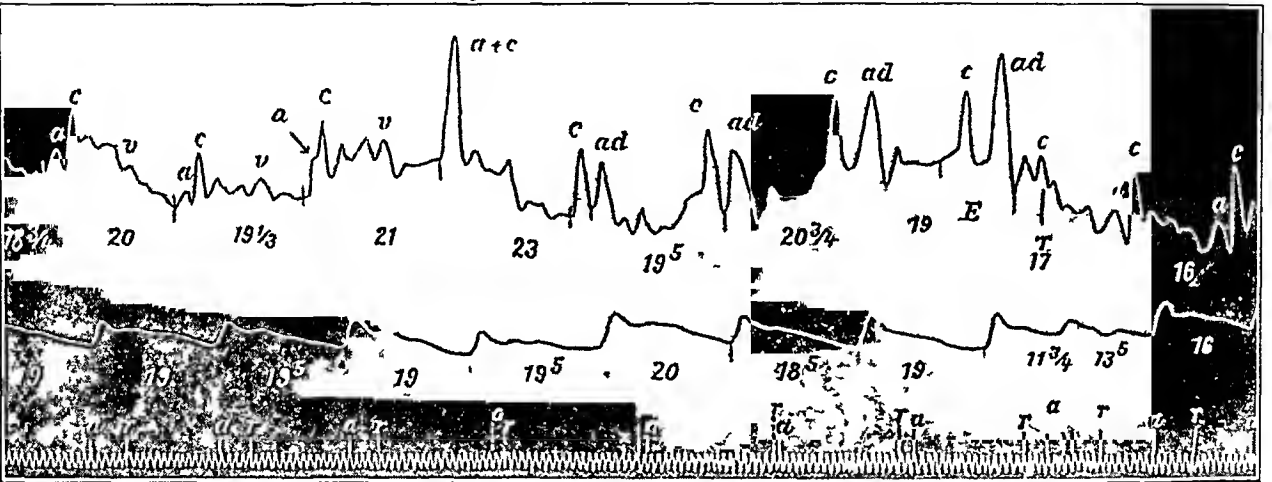


Fig 1—Polygram published in 1906 by Wenckebach showing nodal rhythm, with progressive lengthening of interval between ventricular (*c*) and auricular (*a*) waves. At *E* the auricular wave comes after the refractory period of the ventricle and a reciprocal beat (*c* and on the radial pulse curve) follows.

4 Gallavardin, L., Dufourt, P., and Petzetakis. Automatismes ventriculaires intermittents, *Arch mal du coeur* **7** 1 (Jan) 1914.

5 White, P. D. A Study of Atrioventricular Rhythm Following Auricular Flutter, *Arch Int Med* **16** 517 (Oct) 1915.

6 White, P. D. The Bigeminal Pulse in Atrioventricular Rhythm, *Arch Int Med* **28** 213 (Aug) 1921. Jones, T. D., and White, P. D. Atrioventricular Nodal Rhythm, *Am Heart J* **2** 266 (Feb) 1927.

7 Gallavardin, L., and Gravier, L. Bradycardie nodale permanente, *Arch mal du coeur* **14** 71, 1921.

8 Wilson, F. N. The Production of Atrioventricular Rhythm in Man After the Administration of Atropine, *Arch Int Med* **16** 989 (Dec) 1915.

9 Bishop, L. F. Specific Action of Atropine in Relieving Certain Irregularities of the Heart Beat, *J A M A* **77** 33 (July 2) 1921.

case of nodal rhythm in which bigeminy occurred as a result of atropine medication. He, like Gallavardin, regarded the couple as due to a normal beat interpolated in an atrioventricular rhythm. Peters¹⁰ considered the second beat as a "sinus extrasystole." The reciprocal rhythm, so named by Drury, differs from the reciprocating rhythm of Mines in that the mechanism is not constant but consists of a single ventricular response to an auricular beat arising from the atrioventricular node and occurring late in relation to the ventricular beat which originated simultaneously. In both reciprocal and reciprocating rhythm, partial conduction in both directions is postulated to account for the return of an impulse over a pathway which it has just traversed. Part of the conduction system must be refractory during conduction in one direction, and part during conduction in the opposite direction.

White found that atropine increased the rate of the atrioventricular rhythm without affecting the coupling, the fast rate leading to a prolonged R-P interval. This is confirmed by the action of atropine in Bishop's case and in our own. In one case,⁷ the coupling resulted from a prolonged R-P interval due to vagal stimulation. In our case vagal pressure diminished the tendency to coupling. The disturbance of vagal and sympathetic tone necessary for the occurrence of atrioventricular rhythm seems to vary from case to case. Although vagal release seems to be the most constant cause, increased vagal tone (by digitalis or ocular pressure) is at times an effective agent. It seems reasonable to believe that the same factors which cause nodal rhythm will lead to reciprocal rhythm if they act more intensely, for the greater the atrioventricular rate and the degree of retrograde block, the more often will reciprocal beats occur.

In the case to be described, the sequence of events is of interest. Auricular tachycardia was present for twenty-two days, then nodal and reciprocal rhythm appeared when the patient was fully digitalized and gradually reverted in four days to sinus rhythm. Eight days later, there was a recurrence of persistent nodal and reciprocal rhythm. The variation in degree of bundle branch block in the reciprocal beat is also noteworthy. Its occurrence in couples of shorter duration and its absence in those which are longer is significant of the critical state of the entire conduction system during reciprocal rhythm.

REPORT OF CASE

The electrocardiographic records to be described were obtained during a severe break in compensation of a woman, aged 38, who for ten years had evidence of heart disease due to mitral stenosis. Although ascites, hepatic enlargement and cyanosis were marked, orthopnea was notably absent at all

¹⁰ Peters, J. T. Beitrag zur Kenntnis der irregulären Bradycardien beim Menschen, Wien klin Wchnschr 36 1307, 1924

times Palpitation on effort had been present for some time, but a persistent tachycardia during rest and activity first occurred six days before these observations began. Two days before the first records were taken, she had a regular thready pulse, 170 per minute, but on rest in bed a regular rate of 80, occasionally falling to 40 or 60 and then becoming somewhat irregular, was observed. The jugular veins were distended, the jugular pulse was 160 or more. The clinical diagnosis was auricular flutter, mitral stenosis and myocardial insufficiency.

Auricular Tachycardia or Flutter, Partial Heart Block—Electrocardiographic records taken on September 10, 14, 19, 20 and 21 (fig 2) all gave evidence of an abnormal auricular mechanism, with diphasic P waves recurring regularly. The auricular rate over these twelve days varied only between 180 and 186. The ventricular complexes occurred irregularly at all times except on September 19, when the ventricular rate was 90 and the auricular, 180. In all other tracings ventricular responses occurred in response to every second to fourth auricular beat. While it is well recognized that slow auricular flutter may give auricular complexes simulating the normal, it seems more logical when evidence of con-

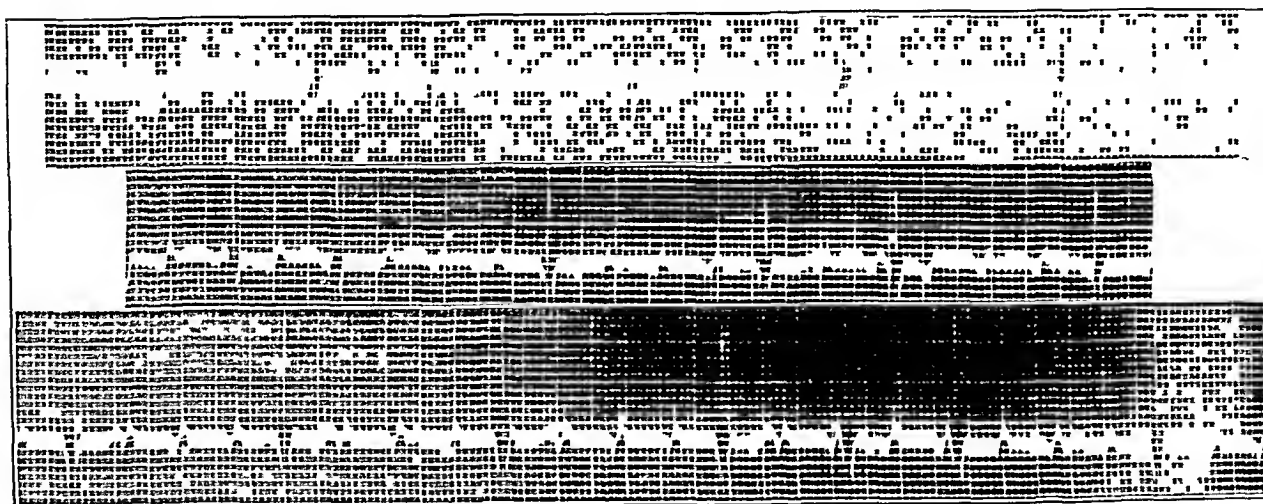


Fig 2—Leads I, II and III of electrocardiogram made on September 10, showing auricular tachycardia, partial heart-block, 4 1, 3 1 and 2 1 rhythm. Auricular rate 186 per minute.

tinuous auricular electrical activity does not occur in any of the leads to consider the disturbance as due to paroxysmal tachycardia rather than to flutter. Vagus and ocular pressure failed to affect the auricle in this case, and these procedures did not increase the degree of block above 4 1. The patient, who weighed only 100 pounds (45.4 Kg), received 18 Gm of powdered digitalis during the first thirty-six hours after the first observation, and 0.2 Gm daily thereafter, without any demonstrable effect except an inversion of the T wave. The records are similar to those in the three patients who had auricular tachycardia with partial block described by White.¹¹

Atrioventricular Bradycardia, Retrograde Conduction and Reciprocating Rhythm—On September 25, the pulse was found to be slow, with occasional coupled beats. Digitalis was discontinued. The total dose in sixteen days was 5 Gm.

11 Sprague, H B, and White, P D. Heart-Block During Auricular Paroxysmal Tachycardia, *M Clin N Amer* 8 1855, 1925.

The electrocardiogram taken the next morning (fig 3) demonstrated a nodal bradycardia, the interval between single ventricular beats indicating a rate of 37 per minute. P waves, resembling the diphasic auricular complex seen during the tachycardia, occurred superimposed on, or directly after, these single beats. Coupled beats predominated, only a few single beats occurring each minute. The couples consisted of a nodal beat with the P wave falling 0.36 or 0.46 seconds after R and on or after T, and a similar Q R S complex from 0.26 to 0.42 seconds after this P wave. The briefer the R-P interval, the longer was the corresponding P-R interval.

During the afternoon (fig 4) the mechanism was practically the same, except that in two instances the P wave, erect and notched, preceded isolated ventricular complexes by 0.12 and 0.19 seconds and the form of the reciprocal Q R S was typical of left bundle branch block in many, but not in all, of the

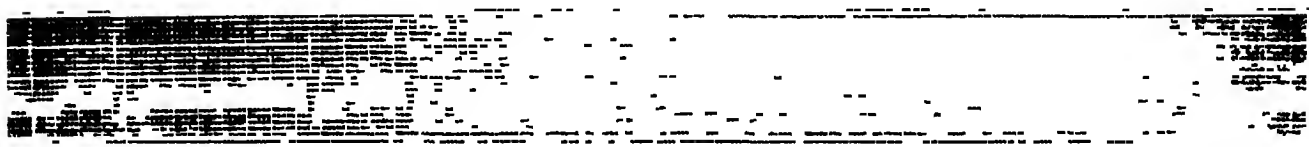


Fig 3—Electrocardiogram made on morning of September 26, showing atrioventricular rhythm and retrograde conduction. The P waves of most nodal beats fall on the T waves and are followed by a ventricular beat. When the P wave falls at the end of the Q R S complex, a reciprocal ventricular beat does not follow. The A-V rhythm has a rate of 37 per minute. The R-P intervals were 0.32 to 0.44 seconds.

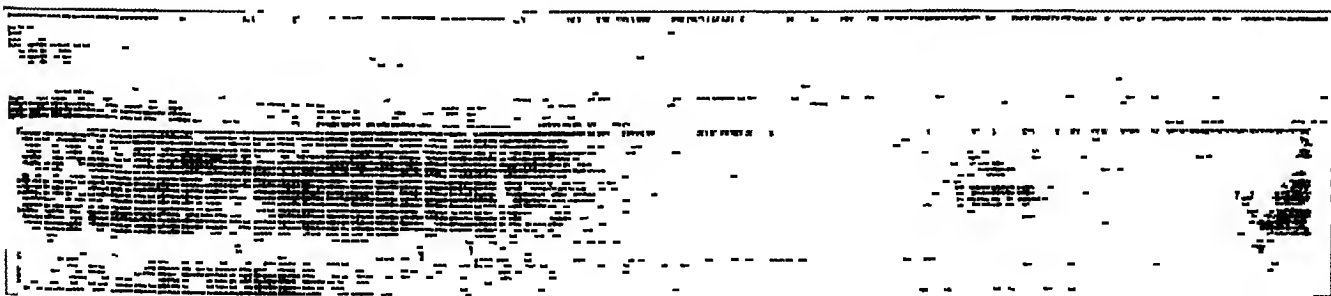


Fig 4—Electrocardiogram made on the afternoon of September 26. In two instances the P wave precedes the nodal Q R S. Inverted T waves are shown.

couples. When the P-R interval was 0.38 seconds or more, a normal ventricular complex followed. On September 27 (fig 5), the nodal rhythm was still present, the rate was 60 per minute and cycles from 4 to 11 beats in length showed the P wave first preceding, then coinciding with, and later falling behind, the Q R S, and finally falling early on the T wave and provoking a reciprocal ventricular response, which occasionally approached the configuration of the left bundle branch block. The P waves preceding the Q R S were erect but deeply notched, those which followed were diphasic. The T waves, inverted on the previous day, were now erect.

The following day (fig 6) short runs of sinus rhythm, with erect, notched P waves, at a rate of 100 per minute, occurred in all tracings, although the predominant feature was nodal rhythm, at a rate of 78 per minute. During the sinus rhythm, the A-V conduction time was 0.2 seconds. When nodal rhythm was present an occasional diphasic P wave preceded the Q R S by as much as 0.16

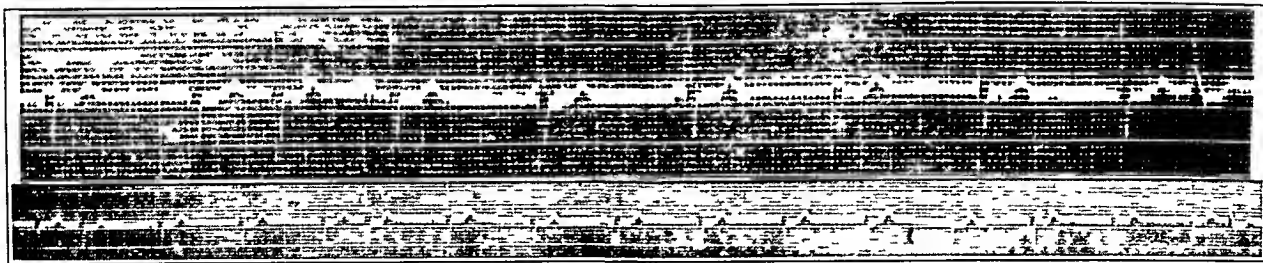


Fig 5—Electrocardiogram made on September 27, showing atrioventricular rhythm with frequent auricular escape. The escape occurs in cycles, commencing after a reciprocal beat, the P-R interval decreasing progressively until retrograde conduction and finally a reciprocal beat occurs and the cycle is repeated. Erect T waves are shown. The mechanism here is similar to that in figure 1.



Fig 6—Leads I, II and III of electrocardiogram made on September 28, showing a condition similar to that in figure 4, but with short runs of sinus rhythm, with a rate of 100. The difference in form of the normal and retrograde P waves is fairly well marked. Erect T waves are shown.

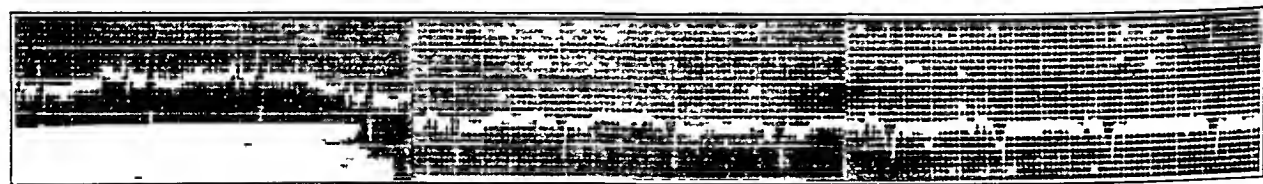


Fig 7—Electrocardiogram made on September 29, showing normal sinus rhythm, right ventricular preponderance, notched P waves and inverted T waves.

seconds. Each subsequent P wave fell later in relation to the ventricular complex, until finally a P wave fell on the T and a reciprocal beat followed. The P-R conduction was 0.32 to 0.40 seconds, and the second ventricular complex was of low voltage. It was followed either by another cycle of nodal rhythm

in which the first P wave again preceded the Q R S, or, more rarely, by a brief resumption of sinus rhythm

On the next day (fig 7) and thereafter for several days normal sinus rhythm, at a rate of 78 or 80 with notched P waves and right ventricular preponderance, was present. This normal mechanism continued until October 6 (fig 8), when a slow rate and coupling were again observed. Electrocardiograms made between September 29 and October 6 showed a normal mechanism, those made on October 6 showed short runs of apparently normal mechanism, with a P-R interval of 0.21 seconds, although the rate was only 50 and suggested an atrioventricular rhythm originating high in the node. These runs of apparently normal beats were rare and terminated in an abrupt change to A-V rhythm, with a rate of 42 per minute and numerous reciprocal beats. The left bundle branch block with the shorter P-R intervals was again present. The patient was given oxygen from a basal metabolism spirometer for seven minutes, during which time the mechanism remained unchanged. Observations made from this time until October 11 constantly showed nodal rhythm, without any more runs



Fig 8—Electrocardiogram made on October 6, showing a slow supraventricular rhythm probably originating in the sinus, although the rate is only 50 per minute. The rhythm abruptly goes over into atrioventricular rhythm, with a rate of 42 per minute with frequent reciprocal beats.

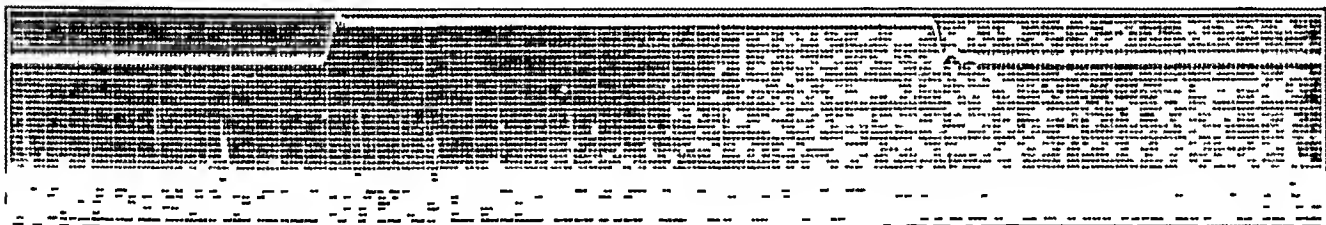


Fig 9—Electrocardiogram made on October 7, showing effect of right vagal pressure. The nodal rate was 46 per minute.

of beats of supraventricular origin. The patient had improved somewhat, and had not received digitalis after September 25. She returned to her home on October 11.

On October 7, observations on the effect of vagal pressure, of atropine and of amyl nitrite were carried out (fig 9). Seven trials of vagal pressure, two left sided and five right sided, demonstrated an immediate slight slowing of nodal rate, an increase in auricular escape and a decrease in coupling. R-P intervals were decreased and P-R intervals lengthened. The effect of atropine (fig 10) was obvious in five minutes and continued for an hour. The atrioventricular rhythm was accelerated, the R-P intervals were longer and more uniform in duration, and the P-R intervals were slightly shorter. Coupling was much more constant, single beats were rare, and auricular escape did not occur. Amyl nitrite, inhaled until giddiness was marked, failed to produce any additional effect one-half hour after atropine was given. These effects are essentially in agreement with those of White and Bishop.

In most cases of reciprocal rhythm variations in the form of the second ventricular complex are noted, but this case seems to be unique in that it demonstrates clearly the relation of the interval between the first and second ventricular complexes to the occurrence of reciprocal beats of aberrant form. Normal ventricular complexes and bundle branch block occur in the same tracings constantly. The block occurs when the interval between the two beats is relatively short, and by measuring the length of the intervals in which block occurs and those in couples with normal intraventricular conduction, one can measure the refractory period of the left branch of the bundle. This varies from day to day. On September 26 the duration of the refractory period lay between 0.64 and 0.69 seconds, on September 27, between 0.47 and 0.55 seconds, on September 28, it was less than 0.44 seconds, on October 6, it was between 0.66 and 0.70 seconds, on October 7, it was between 0.60 and 0.68 seconds. The same relation of aberrant supraventricular complex in the second beat of a couple to the duration of interval between the two beats was noted by Scherf¹² in a case in which coupling presumably was the result of 2:1 sino-auricular block with ventricular escape. The curves that were published seem typical of reciprocal rhythm.

That the conducting system above the bifurcation of the bundle is also in a critical state is demonstrated by the relation between the R-P and P-R intervals of the coupled beats. While the sum of R-P and P-R intervals varies from day

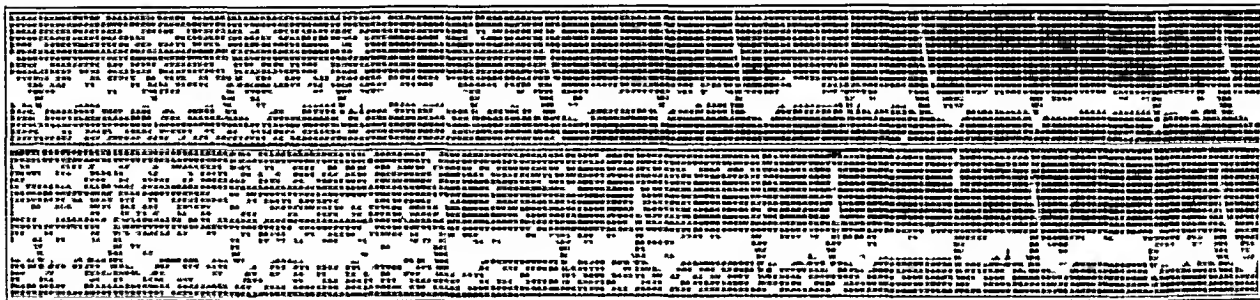


Fig 10—Electrocardiogram made on October 8. The upper tracing was made ten minutes and the lower thirty minutes, after the administration of atropine, 1/50 grain (13 mg) subcutaneously. The nodal rate was 68 per minute.

to day, it is apparent here, as was noted by Scherf¹² experimentally, that the duration of the P-R interval varies inversely with that of the preceding R-P. That part of the conducting system below the site of origin of the nodal rhythm undoubtedly carries both the nodal and the reciprocal impulse, and the rate of conduction in this part of the path of the reciprocal beat probably varies inversely with the time consumed by the impulse going to and returning from the auricle. The double pathway postulated by Drury extends from the site of the pacemaker in the node to the auricle and back again, and it is known that retrograde conduction over this pathway may be slow and varies inversely with the rate of the nodal rhythm. It therefore seems reasonable that the fibers which are refractory to the retrograde impulse will have recovered more completely and conduct more rapidly when the R-P interval is greatest. Hence, the shortening in P-R with lengthened R-P can be a summation of effects in the portions of the path of the reciprocal impulse above and below the site of the pacemaker in the node.

12 Scherf, D, and Shookhoff, C. Experimentelle Untersuchungen "über die" Umkehr Extrasystole, Wien Arch f inn Med 12 500, 1926.

SUMMARY

A case of atrioventricular rhythm is reported in which retrograde conduction and reciprocal rhythm were present, and in which left bundle branch block occurred at times in the reciprocal beat.

The first period of nodal rhythm followed twenty-two days of paroxysmal auricular tachycardia with partial heart block, it lasted four days, and the rhythm gradually reverted to normal. Nodal rhythm recurred in eight days and continued for the six days that the patient remained under observation. The effects of vagal pressure and of the administration of atropine were observed.

EXPERIMENTAL OBSTRUCTIVE JAUNDICE

II MODIFICATION OF THE PARATHYROID TETANY MECHANISM IN JAUNDICE*

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AND

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CHICAGO

Fairly conclusive evidence that one or more of the metabolites arising in obstructive jaundice may produce a functional or structural alteration in some part of the mechanism producing tetany is afforded by the absence or diminution in the neuromuscular response under conditions in which severe tetany would otherwise be evoked. The evidence is threefold. In the late obstructive jaundice of puppies induced by ligation and division of the common bile duct, a marked lowering of the blood serum calcium occurs, which may reach the tetany level¹. Apart from certain intercepting factors, the early precipitation of tetany might be expected in very young animals with severe injury to the liver and disturbance in the intestinal tract. Some apathy and slight depression occur as a rule. As a further test of the foregoing hypothesis,² the parathyroids were removed from animals with obstructive jaundice. In a preliminary report³ of the effect of thyroparathyroidectomy on the jaundiced animals, attention was called to the absence of manifest tetany in more than half of the puppies and the relatively long survival period of the adult animals that showed a marked diminution in the severity of the tetany. By such crucial experiments, we were able to evaluate the parathyroid factor and were led to conclude that the parathyroids had not assumed an added function or were playing some rôle in keeping the animal free from tetany, in so far as jaundiced animals on which parathyroidectomy had been performed also revealed apathy and

* From the Nelson Morris Fund and the John D. and Fannie K. Hertz Fund of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research, and the Department of Physiology of the University of Chicago.

1 Buchbinder, William C., and Kern, Ruth. Blood Calcium Deficiency in Experimental Obstructive Jaundice, *Am J Physiol* **80** 273 (April) 1927, Experimental Obstructive Jaundice. I. Growth Factor in Defective Calcification, *Arch Int Med* **40** 900 (Dec) 1927.

2 Buchbinder, William C., and Kern, Ruth. Blood Calcium Deficiency and Bone Changes in Experimental Obstructive Jaundice, *Am J Physiol* **81** 468 (July) 1927.

3 Buchbinder, William C., and Kern, Ruth. The Effect of Thyroparathyroidectomy on the Jaundiced Animal, *Proc Soc Exper Biol & Med* **25** 3, 1927.

muscular atony and died from what appeared to be circulatory failure. Lastly, the observation of fairly prompt relief from tetany, even though transient, is offered as a third piece of evidence.

METHOD

Fourteen adult dogs were thyroparathyroidectomized after jaundice had been induced by division of the common duct between ligatures. The duration of the jaundice ranged from one to thirty days. The same procedures were carried out on ten puppies from 8 to 10 weeks of age which comprised parts of three litters. Two additional pups, nonjaundiced litter mates, which were thyroparathyroidectomized served as controls.

Blood serum calcium determinations were made in the normal, icteric and subsequent parathyropivic states. In the latter, they were made from every twenty-four to forty-eight hours, so that one could be reasonably assured that parathyroidectomy was complete. The Kramer-Tisdall⁴ technic was employed.

During the normal and icteric states and prior to thyroparathyroidectomy, the animals were fed a stock diet. Following the latter, they were fed solely a diet of cooked meat. For dietary control purposes, a single litter of pups received a ration consisting of cooked cereal, bread and milk.

Collip's parathyroid extract⁵ was administered to three animals. Only one of these exhibited tetany. It received from 20 to 100 units on the eighth, ninth and tenth days after thyroparathyroidectomy. The other two animals received 100 units on the eighth day and subsequently when they became moribund. Eleven days after thyroparathyroidectomy the excretion rate of calcium chloride from the blood stream was determined on the same two animals, following the administration of a 10 per cent aqueous solution of calcium chloride (100 mg per kilogram).

The intravenous injection of dog's whole bile was carried out on two thyroparathyroidectomized animals exhibiting severe tetany. One of these was jaundiced, the other nonjaundiced.

RESULTS

In tabulating the data, it has been considered advisable to refer to the results obtained after thyroparathyroidectomy on three groups of jaundiced animals: the puppies, the adult dogs acutely jaundiced and the adult dogs chronically jaundiced. All of the puppies, except the two controls and most of the adult animals, were jaundiced from sixteen to eighteen days before thyroparathyroidectomy. To avoid confusion, we have referred to these animals as chronically jaundiced.

The survival period after thyroparathyroidectomy for nine chronically jaundiced adult dogs which were untreated and the sole diet of which consisted of cooked meat ranged between one and one-half and seventeen and one-half days. Six of these had a mean survival period

4 Kramer, B., and Tisdall, F. F. A Clinical Method for the Quantitative Determinations of Calcium and Magnesium in Small Amounts of Serum and Plasma, *Bull. Johns Hopkins Hosp.* **32**: 44 (Feb.) 1921.

5 The extract used was parathormone, furnished for the purpose of this investigation by Eli Lilly & Company.

of more than ten days Three died within three days of the operation, one of the latter was a lactating animal Terminal tetany in this group occurred in only two instances Although these animals exhibited a tetany varying in intensity from the mild form in which there was regional muscle fibrillation to a most severe type, the former was much more commonly noted, and in these cases it was intermittent and transient In all instances it was the usual rule to note its complete abatement two or three days before death in whatever type of tetany was displayed, the animal then became stuporous, lethargic and comatose (fig 1 and table 1)

The survival period for the group of ten puppies had a mean average of 38 days, which is slightly longer than the expectancy for animals of this age Three of them lived from five to eight days after thyroparathyroidectomy Three animals exhibited a tetany which



Fig 1—The dog on the left (B1) ten days after thyroparathyroidectomy, showing marked muscular atony and depression This animal lived more than a week after this photograph was taken The blood calcium remained below 4 mg after the tenth day The dog on the right (Daph) is shown twelve days after thyroidectomy in slight tetany

was slight to moderately active, and in only one instance did it appear to be terminal It was much less severe than that observed in the two nonjaundiced thyroparathyroidectomized litter mates that were used as controls On the other hand, the complete absence of manifest tetany was noted in more than half the animals of the series The clinical picture and the survival period were not changed in the one litter which received rations of only milk, cereal and bread

For the group of five acutely jaundiced adult dogs (thyroparathyroidectomized twenty-four hours after division of the common duct) the survival period was a little more than two days The tetany which developed in three of the animals was severe and terminal One of the animals lived ten days, and never exhibited the slightest active tetany

The Time of Appearance and Severity of the Tetany of Jaundiced Thyroparathyroidectomized Dogs and the Blood Serum Calcium*

Calcium

| No Days Lived After Thyroparathyroidectomy | | Days After Thyroparathyroidectomy | | | | | | | | | | | | | | | | | | No days Lived After Thyroparathyroidectomy | |
|--|----|-----------------------------------|---|---------|----------|-----|---|---|---|---|----|----|----|----|----|----|----|----|----|--|--|
| Dogs | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | | |
| ADULT DOGS | | | | | | | | | | | | | | | | | | | | | |
| Sad | 16 | 0 | 0 | ++ (16) | +++ (52) | +++ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Rth | 17 | ++ (70) | + | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Sad | 17 | ++ (78) | + | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Daph | 18 | 0 (71) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Sad | 18 | ++ (77) | 0 | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Bl | 17 | 0 (83) | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Co | 17 | 0 (82) | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Br | 10 | 1 (97) | + | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Lin | 20 | 0 (82) | + | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Lin | 1 | 0 (59) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Lin | 1 | 0 (82) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Spt | 1 | 0 (87) | + | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Nel | 1 | 0 (85) | + | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Wht | 1 | 0 (71) | + | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| PUPPIES | | | | | | | | | | | | | | | | | | | | | |
| Lin | 17 | 0 (79) | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | |
| Lin | 0 | ++ (80) | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | |
| Wf | 18 | ++ (83) | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | |
| Lin | 17 | 0 (79) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Lin | 18 | 0 (82) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Lin | 16 | 0 (83) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Lin | 16 | 0 (87) | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | |
| Spt | 16 | 0 (58) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Wf | 16 | 0 (57) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Lin | 16 | 0 (57) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Lin | 16 | 0 (72) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

I litter received ration of milk, bread, and cereal

* ++, very slight active tetanus, ++, moderate, ++++, severe
 ++ tetanizing infant
 : Nonjuddered controls

I litter received ration of milk, bread, and cereal

* 1, very slight active tetany, 1+, moderate, ++, severe
 1, tetanizing animal
 0, non-tetanic controls

In considering further the symptomatology of the three groups of animals additional observations may be worthy of mention. A peculiar expiratory groan associated with some slight expiratory difficulty but without hyperpnea occurred in all of the puppies. Apart from the hyperpnea occurring in the adult animals a similar respiratory difficulty was noted. The groan, however, was conspicuously absent except in a few instances. Most of the adult animals that lived more than nine or ten days developed decubital ulcers. Although anorexia was marked in several of the dogs, others maintained an appetite that was voracious nearly to the end. In all, a grade of extreme emaciation and cachexia supervened before death. Atony of the sphincters with involuntary urination and defecation occurred at the end. The animals that lived

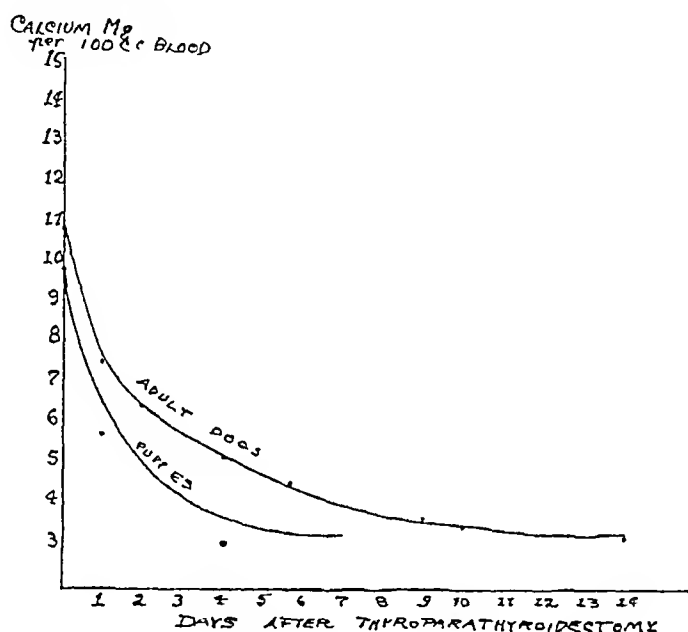


Fig 2—Showing the general trend of the blood calciums in jaundiced-thyroparathyroidectomized animals. Note the more acute drop for the puppy.

for a relatively short time, and especially the puppies which did not exhibit any active form of tetany, appeared to die of an acute poisoning. Retching and vomiting occurred more often in the younger set of animals. Spotting of the stools with blood, the result of an enteritis observed in the pups before thyroparathyroidectomy, was aggravated following this procedure. The adult animals, which uncommonly showed blood in the stools during their jaundiced state almost invariably developed a bloody diarrhea following thyroparathyroidectomy.

There are no significant changes in the level of the blood serum calcium for the adult animals and puppies after a period of jaundice lasting from sixteen to eighteen days. The blood serum calciums of the two groups approximate one another before and after the induction

of jaundice Twenty-four hours after thyroparathyroidectomy, the calcium values of the puppies fall to a considerably lower level than those of the adults (fig 2) Insufficient determinations for the subsequent days do not enable us to draw any conclusions about the trend of the blood calcium in the two respective groups, but there appears to be a more acute lowering in the puppies following thyroparathyroidectomy

Within a few minutes after the intravenous injection of 10 per cent aqueous solution of calcium chloride the blood serum calcium approached that of the normal without the animal exhibiting any change in the picture of extreme apathy and stupor The excretion rate extended over approximately four hours (fig 3) The injection of Collip's parathyroid extract on the same dogs three days before the injection of calcium chloride was carried out revealed the inefficacy of this hormone extract to raise the blood calcium level in the para-

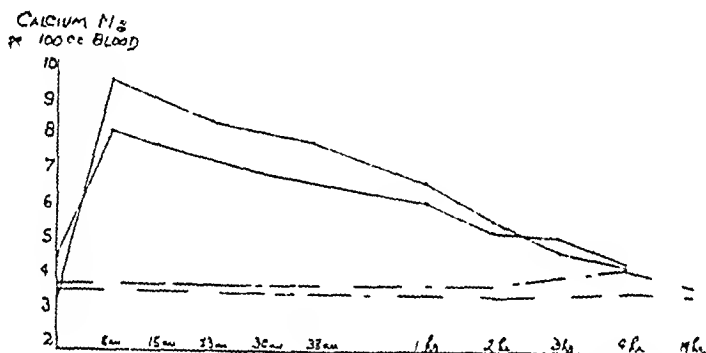


Fig 3—Showing the curve of excretion of calcium chloride and the inefficacy of Collip's parathyroid extract in materially affecting the blood serum calcium in jaundiced-thyroparathyroidectomized dogs The continuous line indicates the excretion of calcium chloride from the blood after intravenous administration of 00100 gm per kilogram (10 per cent aqueous solution) The broken line indicates the curve following the administration of 50 units of Collip's parathyroid extract

thyroidectomized jaundiced animal It did not produce any change in the symptoms at this time, nor did it seem to delay death when the animals became moribund, although it may have hastened it in one instance It was administered to a third animal on the eighth, ninth, and tenth days in doses of from 20 to 100 units, but a progressive lowering of the blood calcium of from 5.0 to 4.2 mg per hundred cubic centimeters of blood occurred until near death, when it rose to 5.7 The tetany in this animal, though not controlled, became less severe, and the terminal picture of extreme stupor was identical with that of the other untreated animals

The intravenous injection of whole bile into two parathyroidectomized dogs, one jaundiced, the other nonjaundiced, was followed by

a relief from the symptoms of tetany. The nonjaundiced animal received 2 cc (injection rate was 1 cc per minute) on the third day after thyroparathyroidectomy when it exhibited marked depression and severe tetany. Two minutes after the injection, the picture changed completely, the animal becoming lively and appearing a little excited, the tetany was completely abolished. Relief from the latter, however, was only transient, and thirty minutes after the injection, the animal developed a seizure. It died the next day of tetany. The jaundiced animal received 12 cc of bile four days after thyroparathyroidectomy. Ten minutes after the injection, it was relieved of tetany, which did not reappear. It died the following day, apparently from an overdosage.

COMMENT

While most of the experimental data already accumulated on the pathogenesis of tetany suggests that either a low concentration of calcium or the action of toxins is responsible for the onset of tetany, the production of an experimental animal with low blood calcium and a toxemia without manifest symptoms of tetany calls for comment. Unless one or more of the metabolites arising in obstructive jaundice may directly or indirectly alter the mechanism of tetany in susceptible animals so as to prevent the appearance of tetany, neither of the current views is adequate to explain the results of these experiments.

For the adherents of the toxin theory of tetany the question is especially pertinent as to why a more acutely fatal outcome does not follow parathyroidectomy at a time when extensive morphologic changes in the liver and injury to the gut have already been wrought, especially when these are superimposed on the already existing toxemia of jaundice. It has been suggested by several investigators that in the parathyroidectomized dog that has adjusted itself to an amenable existence without developing tetany the liver may have taken over the function of the parathyroid glands.⁶ A different opinion has been expressed by Blumenstock and Ickstadt,⁷ who believe that the liver plays the essential rôle in the development of the so-called toxemia of parathyroidectomized dogs. They found that parathyroidectomy in animals in which an Eck fistula had been produced resulted in a delay in the appearance and a diminution of the severity of the characteristic symptoms. Since the syndrome of tetany may be so modified and made less severe under conditions in which there are underlying morphologic changes in or a perversion of function of the liver, it may be postulated

6 Dragstedt, L. R., Phillips, K., and Sudan, A. C. Studies on the Pathogenesis of Tetany. II. Mechanism Involved in Recovery from Parathyroid Tetany, *Am J Physiol* **65** 368 (July) 1923.

7 Blumenstock, J., and Ickstadt, A. A Note on the Role of the Liver in Parathyroid Tetany, *J Biol C* **61** 91 (Aug) 1924.

that this organ may ordinarily, through its unrestricted activity, produce the substances which give rise to the typical syndrome of tetany. In a preliminary report we called attention to some similarity in the symptoms of their animals and those of ours, and, with the evidence obtained from these experiments, we would subscribe to such a view and suggest further that the same products arising from the perversion of liver function in the Eck fistula and in the jaundiced animal may play an active rôle in intercepting the usual nervous phenomena. While parathyroidectomy in a jaundiced animal produces an overwhelming toxemia, the animal lingers, becomes stuporous and dies of what appears to be cardiac failure. The extension of life certainly does not occur by virtue of the insult added to the injury already done, but is probably the result of an ineffectual nervous mechanism which would otherwise abruptly terminate life. In jaundice, the nervous mechanism seems to be protected not only against toxins arising as the end-products of intestinal putrefaction, but also against the extremely low concentration of the blood serum calcium. Calcium administered to such an animal is ineffectual in changing the symptomatology of those which were in a state of severe depression. The excretion rate of calcium chloride from the blood of these animals, however, shows a response that is more nearly comparable to that of a normal animal rather than that described for one jaundiced alone⁸. The cause for this relative loss of calcium-fixing powers which have been ascribed to icteric blood is a matter of surmise apart from its being one of a number of failing physiologic mechanisms. Also the inefficacy of the parathyroid hormone extract in materially affecting the blood serum calcium may be analogous to the failure of response of other gland preparations after their administration under certain conditions⁹.

There has been almost unanimity of opinion that bile acts as a depressant on the central nervous system. Meltzer and Salant¹⁰ concluded that bile contains a tetanic element or an agent which causes increase of excitability of the nervous system as well as depressive elements, and that the two are antagonists. The experiments of Lyon-Caen¹¹ led him to conclude that bile and biliary salts retard muscle

8 Walters, W., and Bowler, J. P. Pre-operative Preparation of Patients with Obstructive Jaundice. An Experimental Study of the Toxicity of Intravenous Calcium Chloride Used in the Preparation of Patients, *Surg Gynec Obst* **39** 200 (Aug) 1924

9 Strouse, S., and Schultz, O. T. Insulin in Diabetes Complicated by Infection, *J A M A* **80** 1592 (June) 1923

10 Meltzer, S. J., and Salant, William. Studies on the Toxicity of Bile. II The Toxic Effects of Bile Upon the Central Nervous System and the Elimination of Strychnine Through the Bile in Nephrectomized Animal, *J Exper Med* **8** 127 (Jan) 1906

11 Lyon-Caen, I. Action de la bile et des sels biliaires sur l'excitabilité neuromusculaire, *Compt rend Soc de biol* **93** 237 (June) 1925

chionaxia while nerve chionaxia remains unchanged. Our own observations indicate that the immunity of the neuromuscular mechanism is more evident when the jaundice is of some duration. In most instances, the acutely jaundiced animal develops a rapid and severe terminal tetany. While up to the present attention has been directed to the striking way in which the effects of jaundice may alter the typical syndrome that follows thyroparathyroidectomy, a consideration as to how the latter may affect the jaundiced state must not be omitted.

In view of the fact that the symptom-complex following parathyroidectomy of the jaundiced animal is parallel in so many ways to that which would accrue in the icteric animals which were allowed to die of a terminal cholemia, parathyroidectomy might be looked on as a hastening process. The listlessness, languor, stupor and coma that supervene before death are alike in both conditions. We must therefore consider that parathyroid failure may enter as a cause of death in the jaundiced animal, especially in the young one which may live well over 100 days after ligation of the common duct and in which a progressive lowering of the blood serum calcium to low levels occurs, but that tetany does not occur because of some compensating mechanism that develops with chronicity, as suggested by Prof. A. J. Carlson. When the very young animal is parathyroidectomized only twenty days after ligation of the common duct, glands more physiologically active are removed, hence the slight or masked symptoms of tetany and the relatively premature death. Such a theory of parathyroid failure seems less applicable for the adult animal, in which normally constant calcium values obtain throughout the course of obstructive jaundice. But the survival period of the puppy after ligation of the common duct is much longer than that for the adult animal, and the marked lowering of the blood serum calcium in the former occurs only late in the obstructive jaundice, at a time when the adult animal would long since have been dead.

The relief of symptoms of tetany following the intravenous injection of bile is of interest, but further experimentation with the biliary constituents will have to be carried out before its bearing on the absence of tetany in jaundice is ascertained. The action of circulating bile may be similar to that of peptone, which Carlson¹² has noted produces a temporary suppression of tetany and for which some depression of the nervous tissues was suggested as the probable mechanism. It is possible, too, that bile produces its effects through a change in the p_H of the blood.

12 Carlson, A. J., and Jacobson, Clara. Further Studies on the Nature of Parathyroid Tetany, *Am J Physiol* 28: 133 (June) 1911.

SUMMARY AND CONCLUSIONS

1 There is a marked diminution generally or an absence of tetany following thyroparathyroidectomy on jaundiced adult dogs and puppies

2 The survival period after thyroparathyroidectomy is prolonged especially for animals that have been jaundiced for some time

3 The acutely jaundiced dog is more susceptible to a severe and terminal tetany

4 Indirect evidence is presented of a functionally or structurally altered mechanism of tetany in obstructive jaundice. This is threefold and is based on (a) the response of the thyroparathyroidectomized animal, (b) the relief of tetany by the intravenous injection of bile, and (c) the absence of tetany in late obstructive jaundice in puppies in which the blood serum calcium may reach the tetany level

5 It is thought that the threshold of nervous excitability is raised in obstructive jaundice. This is in harmony with the belief that bile acts as a depressant for the central nervous system, concerning which there has been almost unanimity of opinion

Book Reviews

THE HARVEY LECTURES, 1925-1926 SERIES XXI Price, \$4 Pp 229, with illustrations Baltimore Williams & Wilkins Company, 1927

The present series of the Harvey Society Lectures is fully up to the usual standard, consisting as it does of reviews on anatomy, histology, physiology, biochemistry and physicochemistry, mathematics, and medical history by authorities representing more or less equally American and European schools

F R Nager of Zurich, the first otologist to deliver a Harvey Lecture, emphasizes the importance of histologic work in diseases of the ear, especially those of the middle ear, in regard to tuberculosis, malignancy, cholesteatoma, otosclerosis and experimental noise-deafness In the last, air conduction is to blame for the degenerative changes in the organ of Corti The histology of the labyrinth is difficult to study in man because of early postmortem changes, but the available work is reviewed

The lecture by J H Northrop of the Rockefeller Institute on the "Dynamics of Pepsin and Trypsin" seems to have dispelled definitely another mystery of so-called colloid chemistry as regards the explanation of enzyme action In a series of beautiful, critical experiments in which changes in the viscosity or conductivity of a solution were used as a measure of the rate of reaction of enzymes, an inverse linear relationship was found between the time it took for a small change in viscosity and the concentration of the pure enzyme The law of mass action was found to hold quantitatively for action of the "inhibitors"—peptone, plasma—so that one could assume that

$$\frac{[\text{free trypsin}] [\text{free inhibitor}]}{[\text{trypsin-inhibitor}]} = \text{a constant}$$

The agreement between observed values and those calculated from the equation was proved in a series of experiments arranged to control separately the concentration of enzyme and inhibitor

The study of the spontaneous deterioration or inactivation of the enzymes demonstrated again the correspondence with the mass law, if one took into account the "free," that is, uncombined with inhibitor, active enzyme The combined form is stable but dissociates into the active enzyme on dilution, just as the salt of a weak acid and base undergoes hydrolysis

The kinetics of trypsin is extremely complicated, but Northrop could show agreement with monomolecular time-curves under proper experimental conditions Thus the velocity of digestion of casein by trypsin at any time depended solely on the concentration of the active enzyme at that time Much evidence is adduced against the catalytic theory, and equations are derived to explain why Schutz's rule holds within a certain range only

The close relationship between the titration curves of proteins and their rate of digestion and the influence of p_H , point to the conclusion that only the protein anion is attacked by trypsin, the cation by pepsin Trypsin itself behaves exactly like a monovalent cation in a Donnan-ratio experiment from p_H 2 to 10.2, beyond that as an anion, pepsin behaves as an anion below p_H 6 No compound is formed between the enzyme and the protein The enzyme is completely ionized Hence enzymes behave exactly as many other simpler chemical substances, and the complex nature of their reactions is due entirely to the fact that several reactions occur simultaneously—a fact not sufficiently appreciated nor properly controlled until this work by Northrop

In the next lecture, W H Lewis of the Carnegie Institution of Washington, discusses the transformation of mononuclear blood cells into macrophages, epithelioid and giant cells, bringing forward strong evidence in support of the

monistic view. The vitally stained hanging drop of whole blood—blood cultures on a cover slip—and spreads of living tissue were the methods used. The work is entirely convincing to the reviewer, so also is that of Sabin, Carrel and Maximow whose views are energetically disputed by Lewis. When such authorities disagree on fundamental grounds, interesting work may be expected in the future.

J. B. Collip of the University of Alberta gives an excellent review of the anatomy, physiology and pathology of the parathyroid glands including a discussion of clinical forms of tetany. He then presents his own brilliant researches culminating in the extraction, isoelectric purification and standardization of the parathyroid hormone, whose specific action consists in elevating the level of blood calcium in normal or parathyroidectomized animals and patients. Tetany may thus be abolished by appropriate parenteral administration of the extract. On the other hand, hypercalcemia—20 mg. or more per hundred cubic centimeters—may be produced, leading to a characteristic syndrome with terminal failure of renal function, marked nitrogenous retention, hyperphosphatemia and acidosis. The blood becomes extremely viscous, and hemorrhages of the mucous membrane are constantly found in the gastro-intestinal tract. Rabbits and rats are resistant to the hormone. Calcium lactate by mouth enhances the action of the hormone reducing the amount necessary in human cases. Satisfactory results have been obtained in clinical hypoparathyroidism. After Collip's work, the guanidine theory of parathyroid tetany has scarcely a leg on which to stand.

"Empiricism and Rationalism" are presented by E. B. Wilson of Harvard University in a keen, illuminating style. Statistical analysis is shown to be essentially descriptive or empirical as contrasted with the experimental method or rationalism. "The place for complicated mathematics is in the follow-up." It is not of much use in the original discovery. The value of mathematics to the scientist is not to teach him formulas, but how to formulate. Wilson points out clearly the limitations of statistical equations, the adjustability of their constants as compared with the fixed constants in some natural laws, and the uselessness of looking for correlations by the statistical method if antecedent rationalism has not been employed. The exact sciences make little use of statistics because good control is available. A plea is made in the case of the beginner in science for qualitative experiments and for a return to the "stubborn facts of nature" instead of juggling with complicated mathematics or highly intricate apparatus.

A scholarly review of the development of modern therapy beginning with the application of the statistical method by Louis in the early nineteenth century to the effects of venesection on various acute diseases, is presented by Knud Faber of Copenhagen who contrasts the Renaissance of clinical entities by Laennec and Bretonneaus with the development of experimental pharmacology by Magendie, who led up to the German physiologic school of medicine. The latter fell short of ideal therapy because it treated the disturbed function and not the specific disease. In the last quarter of the nineteenth century and in the first quarter of the twentieth century the principle of clinical entities has become firmly established through the discovery of the diseases of the ductless glands and those due to specific bacterial invasion. The influence on therapeutics is too obvious to mention, but one must still distinguish between symptomatic therapy and curative therapy. The latter is obtainable only after the disease can be reproduced experimentally.

B. Brouwer of Amsterdam gives the last lecture, dealing with the correlation between comparative anatomy and neuropathology. Striking evidence is brought forward for the division of the cerebellum into the 'neo' and 'paleo' parts, the latter consisting of the vermis, flocculus and paraflocculus. The neocerebellum is less resistant to injurious agencies. The olivary system can also be shown to consist of "neo"- and "paleo"-divisions. The origin of the midline oculomotor nucleus of Perlia is connected with the frontal position

of the eyes and the overlapping of the visual fields, and its close special relationship to the Westphal-Edinger nucleus for pupillary contraction is given as an example of neurobiotaxis. The columns of Goll and Burdach develop phylogenetically with the gnostic or "neo" sensibility as distinguished from "paleo" or vital sensibility, represented chiefly in the gray matter of the posterior horn. The trigeminal nerve has "neo"- and "paleo"- nuclei autonomic functions which belong to the "paleo" system, and are represented by much more complex tracts than the "neo" system. The visual tract extending from the external geniculate body to the occipital cortex is an example of the superimposition of the new system on the old reflex visual pathways to the midbrain, occurring presumably to allow exact visual localization by the higher forms of animal life.

MODERN MEDICINE ITS THEORY AND PRACTICE Volumes 4 and 5 Edited by SIR WILLIAM OSLER, BART, M.D., F.R.S. Reedited by THOMAS McCRAE, M.D., assisted by ELMER H. FUNK, M.D. Third edition, thoroughly revised. Price, \$9 per volume. Philadelphia: Lea & Febiger, 1927.

In volume 4, diseases of the respiratory and circulatory systems are discussed, and in it the high standard of the previous volumes of this series is maintained. While this edition loses none of the charm associated with the list of notable contributors of the original edition, it has been effectively brought up to date. It contains chapters written by Morris, Christian, Hoover, Herrick, Babcock, Howard, Gibson, Osler, Lewis, Maude Abbott and others well known in medical literature. Each chapter covers the subject thoroughly, the whole being a complete general treatise of the diseases of the respiratory and circulatory systems. The chapter on the "Rate and Mechanism of the Heart Beat" by Sir Thomas Lewis is a presentation of electrocardiography stated in simple terms and without undue emphasis on the clinical value of this observed phenomenon and in such terms that the general practitioner can readily grasp it. The chapter on "Congenital Cardiac Disease" by Maude E. Abbott is, in fact, a marvelous and authoritative monograph of this whole field, occupying 200 pages of the present volume, profusely illustrated by photographs of pathologic specimens and diagrams painstakingly gathered together not only by the author but by her colleagues and predecessors at McGill, many of the specimens were collected by Osler himself.

Volume 5 covers diseases of the blood, lymphatic system, ductless glands, kidneys, and vasomotor and trophic disorders by such authorities on these subjects as Richard C. Cabot, Krumbhaar, Warthin, Longcope, Dock, John and Thomas McCrae, Rowntree, O'Hare, Hugh Young, Osler and others. Each chapter is complete and revised to date. A critical survey of the volume impresses one with the thoroughness with which each subject is covered. There is little to criticize. Especially impressive is the rational manner in which the subject of diseases of the ductless glands by George Dock, H. Lissner and Warthin is handled. They are careful and conservative in all statements, yet comprehensive and inclusive of all real advance in this field. The introduction to the diseases of the kidneys by the late John McCrae, revised by Leonard G. Rowntree, covers the recent advances that have been made in experimental medicine which may be applied to clinical medicine. Physicians are gradually establishing a rational conception of the mechanism of the function of the kidney which is of inestimable value when applied at the bedside, notably in the application of therapeutic measures. From this point of view alone the whole part devoted to diseases of the urinary system is well worth studying, especially by those who may not be familiar with recent progress made in the field of physiology of the kidneys and who are unfamiliar with the improvements in therapy as applied to the treatment in nephritis and in the nephroses.

Osler's "Modern Medicine" as represented by the present edition and as a standard system of medicine should find its place on the shelves of every medical library.

SALFROSE UND HYPERTONIE DER INNERVIERTEN ARTERIEN By GUSTAV RIEKER
Price, 10 50 R M Pp 193 Berlin Julius Springer, 1927

In this monograph, Rieker, who is well known for his excellent experiments on the innervation of the blood vessels, discusses in detail his conception of arteriosclerosis and hypertension. Most intensive nervous stimulation causes paresis of the constrictors of the media and stasis in the vessels of the adventitia. Compressed by the blood pressure inside of the vessels, the media is deprived of the nourishing tissue fluids and becomes necrotic. This is followed by sequestration and calcification. Less intensive stimulation leads first to an accumulation of the tissue fluids in the intima, loosening of the intima and hyperplasia of the connective tissue. Weak stimulation, finally results in constriction, narrowing of the lumen and hyperplasia of the media. One condition to which Rieker attributes much importance is the so-called peristasis. Stimulation of medium intensity produces an identical reaction of arteries and capillaries. Stimulation of the dilators leads to fluxion and hyperemia, that of the constrictors to ischemia and anemia. More intensive stimulation reveals the capillaries as the most sensitive part of the circulatory system in that their irritability disappears. At the same time the arterioles and small arteries constrict, thus, the blood passes through narrow arterioles into the wide bed of the capillaries. It flows slowly or even stagnates. These changes are of fundamental importance in many pathologic conditions, especially in nephritis, primary contracted kidney and cerebral hemorrhages.

In his antagonism to Virchow's cellular pathology, Rieker has often been attacked by those who adhere to Virchow's doctrines. Every modern clinician will read this book with much interest. It contains a wealth of thought. There is only one objection, namely, the complicated construction of sentences which Rieker uses and which makes reading difficult even for one familiar with the German language.

HYPOTENSION By ALFRED FRIDLANDER, Professor of Medicine, College of Medicine, University of Cincinnati Price, \$2 50 Pp 193 Baltimore Williams & Wilkins Company

The author has collected a large amount of useful data on this subject and arranged them so that the reader can obtain a clear insight into the present status of hypotension. He has systematically outlined the conditions and diseases in which hypotension occurs. The temporary hypotension observed in surgical shock is duly considered, and the relation of this hypotension to decreased blood volume is discussed. Dehydration in cholera is considered the cause of the decreased blood volume and hypotension. Postural hypotension, on the other hand, is attributed to a disturbance of the vasomotor system.

The author presents in detail the different views regarding the relation of the suprarenals to blood pressure. He accepts the evidence that the suprarenal cortex is the necessary portion of the gland for maintaining normal blood pressure. Addison's disease is considered the most clearly defined clinical example of chronic hypotension. He discusses the lack of uniform benefit following specific glandular therapy in Addison's disease and emphasizes the need for further investigation of the function of the suprarenals before satisfactory therapy can be instituted. The author has not been satisfied merely to compile the known data, but he has examined them critically and has left the stamp of his own interpretation on many of them. The clearcut distinction which he makes between temporary and chronic hypotension is important from the aspects of future experimental and clinical work.

PIONEER MEDICINE IN WESTERN PENNSYLVANIA By THEODORE DILLFP Price, \$3 New York Paul B Hoeber, 1927

This book is a compilation of brief bibliographies of men who, as the title indicates, were prominent in medicine during the early days in western Pennsylvania. To the reviewer the most interesting part of the entire work

is a quotation from the notes of Joseph Doddridge, written in 1824, edited under the direction of Alfred Williams and published by Joel Mensell in 1896. From the extracts of the notes it is evident that Doddridge was a keen observer and possessed considerable dramatic ability in presentation of his material.

The story of these pioneers in western Pennsylvania should be particularly interesting to readers in this locality and to all students of American medical history.

THE NORMAL DIET By W D SANBURN, M D Price, \$1.50 Pp 136 St Louis
C V Mosby Company, 1927

The normal diet, discussed in terms that patients can well understand, is described and illustrated by menus. Chapters are devoted to the bulk requirements of the body, the acid ash type of acidosis, the acetone type of acidosis, the caloric, the protein, the mineral, the vitamin and the water requirements of the body. The author believes that the acid ash foods bear a relation to high blood pressure. He states that in a series of fifty cases, there was a drop of from 40 to 50 points in 90 per cent, after the patients were put on the proper "basic" diet. Blood pressure usually has a considerable fluctuation, and it would be interesting to follow a similar number of cases over the same period of time in which treatment was not given.

MEDIZINISCHE PRAXIS — SAMMLUNG FÜR ARZTLICHE FORTBILDUNG Volume II —
Die Magengeschwurskrankheit — Pathologie und Therapie vom Standpunkt
des Internisten Von Priv Doz Dr Harald Ohnell, Krankenhaus Sabbats-
berg, Stockholm Price, 5 R M Leipzig Theodor Steinkopff, 1927

This is a seventy-five page illustrated monograph in which the etiology, pathology, symptoms, diagnosis and treatment of gastric and duodenal ulcer are briefly considered. Its purpose is to present a practical discussion of the subject in a form sufficiently concise for the use of the general practitioner. It does this extremely well.

ANGINA PECTORIS

A SYNDROME CAUSED BY ANOXEMIA OF THE MYOCARDIUM¹

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CHICAGO

AND

WILLIAM H RESNIK, M D

STAMFORD, CONN

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Summary and Conclusions

In spite of the fact that angina pectoris has been known for over a century and a half, there is still a lack of unanimity regarding its cause. In this paper we will present a theory which, we believe, offers a logical answer to the problem. It is not our purpose to make any pretense at a comprehensive review of the extensive literature dealing with this question. We shall limit ourselves more or less closely to a consideration of those facts and views concerned with the problem that conform to the present ideas of anatomy and physiology.

DEFINITION OF ANGINA PECTORIS

In a discussion of angina pectoris, it is absolutely essential that there be a clear understanding of what is meant by the term. No doubt much of the confusion concerning the nature of the condition has been due to the absence of a well recognized and uniform pathologic basis for the condition. This state of affairs has permitted a certain degree of looseness in the clinical conception of the condition, since no absolute criterion was at hand even at autopsy to prove whether angina pectoris

¹ Read at the New York Academy of Medicine, Section of Medicine, April 17, 1928

had or had not been present during life. The result has been the inclusion under the term *angina pectoris* of cases which differ considerably among themselves, and which often have as their only common feature the occurrence of pain or discomfort in the region of the heart. Expressions like "pseudo-angina," "reflex angina," "vasomotor angina" and "secondary angina" have been coined to cover the various types of cardiac pain which bear more or less resemblance to the "true" angina. To some, *angina pectoris* is practically synonymous with "heart pain," merely a symptom complex elicited by a wide variety of conditions. To them *angina pectoris* does not stand for a clear and well defined clinical picture, at times it may have the terrible significance that is commonly attached to the term, at other times it does not have any other significance than the expression in pain of an entirely benign condition.

We feel that such a conception of angina is entirely erroneous. The fact remains that out of the confused *mêlée* of clinical conditions to which the term "*angina pectoris*" has been applied, one condition stands forth, clearly marked from the others. It is the one that corresponds to Heberden's original description, and its import is unmistakable: the patient with this condition is doomed.

But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and the sense of strangling, and anxiety with which it is attended, may make it not improperly to be called *angina pectoris*.

Those who are afflicted with it are seized while they are walking (more especially if it be up hill, and soon after eating), with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue, but the moment they stand still, all this uneasiness vanishes.

In all other respects the patients are at the beginning of this disorder, perfectly well, and in particular have no shortness of breath from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the *os sterni*, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm, as I have had opportunities of observing by feeling the pulse during the paroxysm. Males are most liable to this disease, especially such as have passed their fiftieth year. After it has continued a year or more, it will not cease as instantaneously upon standing still, and it will come on not only when persons are walking, but when they are lying down.

Some have been seized while they were standing still or sitting, also upon first waking out of sleep.

The termination of the *angina pectoris* is remarkable. For if no accident intervenes, but the disease goes on to its height, the patients all suddenly fall down, and perish almost immediately.²

In this masterly description of Heberden's, are found the essential features of *angina pectoris*. It is the condition depicted therein that we

2 Heberden, William. Commentaries, p. 292.

wish to discuss, and to which the term "angina pectoris" rightfully belongs. It is characterized by (a) paroxysmal pain, usually pectoral, provoked by an increase of the demands on the heart and relieved by a diminishing of the work of the heart, and (b) the likelihood of termination by sudden death.

The pain is brought on by effort. By effort, we mean anything that demands more work of the heart than is imposed on it at rest. This may be actual muscular exercise, such as walking. Since climbing an incline places a greater burden on the heart than walking on a level, the pain usually shows itself first when the patient mounts a flight of stairs or climbs a hill. The pain is even more easily produced when the muscular exercise is undertaken against a wind, in the cold or after a hearty meal. Emotion alone may precipitate an attack. But whatever may be the stimulus that calls forth a paroxysm of pain, it is always one that increases the work of the heart. The pain is usually substernal, but it may be referred to the precordia or epigastrium, it often radiates to the upper extremities, or jaw, or to more remote areas of the body, and may, indeed, be felt only here. Early in the disease it may be described as a sense of oppression, but when it becomes well marked, it is, characteristically, constrictive. The pain is rapidly relieved by rest, and is often accompanied by a sense of impending dissolution, the "angor animi" on which so much stress was laid by Allbutt and Huchard. The anguish is described (Allbutt³) as being "even in slight or incipient cases, an organic dread or sense of ill-omen, as contrasted with rational apprehension," "a strange indescribable fear."

The condition is likely to end in sudden death. Any hypothesis that attempts to explain the nature of angina pectoris must account for this remarkable feature of the disorder. The likelihood of sudden death is the one distinguishing feature that differentiates "true" angina from all forms of "false" angina. The lack of appreciation of this point as a cardinal characteristic of the disease has led to the confusion of Heberden's angina with other types of cardiac pain that should never have been called angina pectoris. The likelihood of sudden death is a feature that is indissolubly linked with the underlying mechanism of the disease. Only by including in angina pectoris such cases as are "likely to end in sudden death" does one isolate those cases that correspond to the original description of the disease, and eliminate the cases that bear only a more or less close resemblance to Heberden's angina. It is, of course, impossible, in a given instance, to predict with absolute certainty the ultimate outcome of the case, but when the diagnosis "angina pectoris" is made, there should automatically be the implication

3 Allbutt, Sir Clifford. *Diseases of the Arteries, Including Angina Pectoris*, ed. 1, New York, The Macmillan Company, 1915, vols. 1 and 2.

that the patient may, and probably will, die suddenly. We shall later explain in more detail our reason for making the likelihood of sudden death such an integral feature of the definition of the disease.

The foregoing characteristics, then, are those that distinguish angina pectoris from other types of cardiac pain. It must be stated that certain exceptions exist. On occasion, the pain of true angina pectoris may arise spontaneously, as during sleep, that is to say, without provocation of one of the usual stimuli—muscular effort, cold, emotion or a hearty meal. But even these exceptions are probably more apparent than real in many cases. In some instances, the pain may not subside on rest, or the outcome is not sudden death. In fact, actual cure may take place. These exceptional instances will also be discussed later.

All the other manifestations that may occur in angina pectoris are of minor importance—changes in respiration, in blood pressure, in heart rate and rhythm, in the vasomotor system, of posture, etc. They are inconstant and do not belong to the major picture.

THE PATHOGENESIS OF ANGINA PECTORIS

It is our belief that angina pectoris is always due to anoxemia of the myocardium, that is, the attack occurs when the oxygen supply to the heart is inadequate to meet the oxygen demands of the heart. In the usual case of angina, the anoxemia is relative, being sufficient for the needs of the heart at rest and insufficient when the work of the heart is increased. In acute coronary occlusion, however, the anoxemia is absolute, since the oxygen supply is inadequate even when the heart is at rest.

All cases of genuine angina have anoxemia of the myocardium as their basis, nevertheless, anoxemia of the myocardium may exist without causing angina, and it must be confessed at once that all factors determining whether or not angina will develop are not clear. Thus, anoxemia may be present in congenital heart disease or pernicious anemia, for example, and yet angina is extremely rare in these conditions. It would seem that when anoxemia affects all the tissues of the body as well as the heart, or when the heart is uniformly affected, so far as one may judge, angina is usually absent. When the heart is affected in such cases, the symptoms are practically always those of so-called congestive heart failure. On the other hand, angina tends to appear when, in spite of anoxemia being present, the contractile power of the heart remains good, evidenced by more or less complete freedom from dyspnea or other symptoms of a failing myocardium. These conditions occur most commonly when only a restricted part of the heart muscle suffers from lack of oxygen, as in coronary sclerosis, the remainder is relatively uninvolved and hence the contractile power of the heart remains good. There are exceptions to these rules—there

are rare instances of angina pectoris in patients with pernicious anemia, and a patient with coronary sclerosis may suffer only from so-called congestive heart failure, angina never appearing

The idea of anoxemia as the cause of angina is not new. All coronary theories are based on the contention that ischemia of the heart muscle is the cause of angina. "An author who would wish to appropriate for himself, with respect to the priority of this (coronary) theory, the labor of a whole century, would commit an injustice for his own profit" (Huchard⁴). However, the idea of coronary spasm has been incorporated in practically every recent theory that attributes angina to ischemia, and we shall show that such an idea must be regarded with skepticism. It is possible, however, to demonstrate anoxemia in all genuine cases of angina pectoris, without resorting to a theory of such questionable validity.

THE PATHOLOGY OF ANGINA PECTORIS

The pathologic conditions associated with angina pectoris may be grouped as follows:

- 1 Coronary disease
 - (a) Sclerosis of the coronary arteries, with or without complete obstruction
 - (b) Occlusion or encroachment of the mouths of the coronary arteries by either syphilitic aortitis or arteriosclerosis
- 2 Aortic insufficiency
- 3 Miscellaneous conditions

Coronary disease and aortic insufficiency make up the vast majority of cases, as will be seen from tables 1 and 2.

Of the cases of angina pectoris that we have personally observed thirteen have come to necropsy, table 1 summarizes the pathologic observations. All the patients had either coronary disease or aortic insufficiency: five had coronary disease alone, five had aortic insufficiency alone and three had combined coronary disease and aortic insufficiency. Table 2 gives the important pathologic data in other series of cases taken from the literature, and again the preponderant rôle that coronary disease and aortic insufficiency play is well illustrated.

Coronary Disease—But few words need be devoted to the subject of coronary disease. Aside from the question of involvement of the aorta, there is not any doubt that the commonest lesion by far in cases of angina pectoris is coronary disease. This fact is sufficiently well recognized to render further comment unnecessary. The production of anoxemia of the heart by such a lesion is, of course, clear. We merely wish to call attention to the important work of LeCount⁵ who

4 Huchard, H. *Traite clinique des maladies du coeur et des vaisseaux*, Paris, 1893, p. 610.

5 LeCount, E. R. *Pathology of Angina Pectoris*, J. A. M. A. **70**: 974 (April 6) 1918.

reported sixty cases in which death resulted from disturbance of coronary circulation or from lesions generally regarded as caused by such difficulty. Of 175 patients who died from heart disease, only those with coronary disease had had symptoms indicative of angina pectoris.

TABLE 1—*Authors' Cases of Angina Pectoris, Observations at Necropsies*

| Conditions Observed | No. of Cases |
|--|--------------|
| Coronary occlusion of one of the main branches | 4 |
| Extensive coronary sclerosis without complete occlusion | 1 |
| Syphilitic aortitis with aortic insufficiency (occlusion of the left coronary ostia in 2 cases) | 5 |
| Rheumatic aortic insufficiency (one case complicated by subacute bacterial endocarditis) | 2 |
| Aortic stenosis and insufficiency with narrowing of coronary orifices at their origin in the aorta | 1 |
| Total | 13 |

TABLE 2—*Pathologic Observations in a Series of Cases Taken from the Literature*

| Author | Total Cases | Coronary Disease | Aortic Insufficiency | Remarks |
|---|-------------|------------------|----------------------|--|
| Huchard <i>Traite clinique des maladies du coeur et des vaisseaux</i> , Paris, 1893, p. 610 | 145 | 145 | Not mentioned | |
| Osler <i>Lancet</i> 1 637, 839 and 973, 1910 | 17 | 14 | 1 | (a) One case. Coronaries were small. (b) One "negative" case. |
| Thayer <i>Internat Clin</i> 1 1, 1923 | 24 | 19 | Not mentioned | (a) One case with myocardial scars. (b) Four cases with syphilis of aorta the only obvious lesion. |
| Mackenzie <i>Angina Pectoris</i> , London Oxford University Press, 1923 | 22 | 18 | 5 | (a) Two cases with muscular changes such as one encounters in coronary disease. Exact state of coronaries not given. |
| Braun <i>Wien klin Wchnschr</i> 39 265 and 304, 1926 | 127 | 127 | — | |
| Oberndorfer <i>München med Wchnschr</i> 72 1495, 1925 | 17 | 17 | — | |
| Gallavardin <i>Les angines de poitrine</i> , ed. 1, Paris, Masson & Co, 1925 | 14 | 13 | 0 | (a) One case with "azotemic" nephritis. |
| Pauli <i>Ztschr f Kreislaufforsch</i> 19 163, 1927 | 20 | 20 | 2 | |
| Present series | 13 | 8 | 8 | |
| Total | 399 | 381 | 19 | |

Aortic Insufficiency.—Although aortic insufficiency ranks far behind coronary disease in incidence, this lesion is found in the bulk of the cases of angina pectoris not associated with coronary disease. Often the two conditions occur together, particularly when both are caused by syphilitic aortitis. The striking frequency with which aortic insufficiency is accompanied by angina has long been recognized and emphasized by

Nothnagel,⁶ Neusser,⁷ Fraenkel,⁸ Osler,⁹ Gallavardin,¹⁰ Longcope,¹¹ Mackenzie¹² and others Lord¹³ stated that in five of his six cases of angina occurring in syphilitic patients there was aortic insufficiency Gallavardin found that of his cases of angina with aortic insufficiency 87 per cent were of syphilitic origin

Mackenzie observed angina pectoris in ninety patients with aortic insufficiency, 23 per cent of the total number of cases reported It is not clear how many of his cases were due to syphilitic aortitis In some, in which postmortem records are available, the coronary arteries were normal, in others, some degree of obstruction of the coronary arteries was present, either by narrowing of the orifices or sclerosis of the vessels Of our own cases of angina, seven occurred in patients with syphilitic aortic insufficiency Of these latter patients, five came to necropsy, and in two there was partial occlusion of the coronary arteries Among other authors who mention the occurrence of angina in cases of syphilitic aortitis and aortic insufficiency may be mentioned Longcope,¹¹ five cases, and Lamb,¹⁴ ten cases

Although it is true that when angina pectoris develops in a patient with aortic insufficiency, the valvular lesion is usually of syphilitic origin, angina is also seen in instances of rheumatic aortic insufficiency We have observed four patients with this type of valvular disease who suffered from seizures of angina, in the one case in which necropsy was performed, the coronary arteries were patent In a group of thirty-three cases of aortic insufficiency in young persons, in which the history of rheumatic infection was positive in 87 per cent, Clark¹⁵ found that "many of the patients suffered from attacks of angina pectoris" Allbutt referred to similar cases, and other instances were recorded by

6 Nothnagel, H. *Schmerzhaftes Empfindungen bei Herzerkrankungen*, Ztschr f klin Med **19** 209, 1891

7 Von Neusser, E. *Angina Pectoris*, New York, E B Treat & Co, 1909; trans into English by Andrew MacFarlane

8 Fraenkel, A. *Angina Pectoris*, Kong f inn Med **10** 228, 1891

9 Osler, William. *Angina Pectoris*, Lumelien Lectures, Lancet **1** 697 (March 12) 1910, **1** 839 (March 26) 1910, **1** 973 (April 9) 1910

10 Gallavardin L. *Les Angines de Poitrine*, ed 1, Paris, Masson & Cie, 1925

11 Longcope, W T. *Syphilitic Aortitis Its Diagnosis and Treatment*, Arch Int Med **11** 15 (Jan) 1913

12 Mackenzie, Sir James. *Angina Pectoris*, London, Oxford University Press, 1923

13 Lord, F T. Discussion, Tr A Am Phys **42** 53, 1927

14 Lamb, A R. *Syphilitic Aortitis and Aneurysm of the Aorta* in Nelson's Loose Leaf System of Medicine, New York, Thomas Nelson & Sons, 1924, vol 4, p 531

15 Clark, J W. Some Features of Aortic Regurgitation in Young Subjects, Brit M J **1** 1364 (June 10) 1911

Coombs,¹⁶ Levine,¹⁷ Gallavardin,¹⁰ Cutler and Fine,¹⁸ Wenkebach,¹⁹ White and Mudd²⁰ and others

Angina has also appeared in rare cases of rupture of the aortic valve (Hirschfelder²¹ and Herrick and Nuzum²²) In Hirschfelder's case, the coronary arteries were normal

Various hypotheses have been advanced to explain the occurrence of angina in cases of aortic insufficiency Since most of the cases were associated with syphilitic aortitis, the latter condition was held responsible by Allbutt for the attacks of angina Nevertheless, he confessed that he was unable to account for the angina in instances of rheumatic aortic insufficiency in which the aorta was normal Fraenkel held that changes in the intraventricular pressure probably played a rôle in causing the angina, and Mackenzie attributed the attacks of pain to some peculiar innervation of the heart in aortic regurgitation None of these explanations are satisfactory or based on fact We feel that modern experimental evidence has furnished a more logical explanation for the occurrence of angina in cases of aortic insufficiency

Lewis and Drury²³ first demonstrated that the circulatory changes taking place in arteriovenous fistula were similar to those seen in aortic regurgitation, namely, low diastolic pressure, high pulse pressure, water hammer pulse, collapsing pulse, etc They presented evidence to show that these signs were dependent on a leak of blood from the arterial stream and suggested that the same was true in cases of aortic reflux Since the coronary blood supply is dependent for the most part on the height of the diastolic blood pressure, and since in aortic insufficiency the diastolic pressure is characteristically decreased, it was reasonable to suppose that a diminished coronary flow was present in cases of aortic

16 Coombs, C P Rheumatic Heart Disease, ed 1, New York, William Wood & Co, 1924

17 Levine, S A Angina Pectoris (Some Clinical Considerations), J A M A **79** 928 (Sept 16) 1922

18 Cutler, E C, and Fine, Jacob Sympathectomy in Angina Pectoris, J A M A **86** 1972 (June 26) 1926

19 Wenkebach, K F Angina Pectoris and Possibilities of Its Surgical Relief, Brit M J **1** 809 (May 10) 1924

20 White, P D, and Mudd, S G Angina Pectoris in Young People, Am Heart J **3** 1 (Oct) 1927

21 Hirschfelder, H Diseases of Heart and Aorta, ed 3, Philadelphia, J B Lippincott Company, 1918, p 388

22 Herrick, J B, and Nuzum, F R Angina Pectoris, J A M A **70** 67 (Jan 12) 1918

23 Lewis, T, and Drury, A N Observations Relating to Arterio-Venous Aneurysms Circulatory Manifestations on Clinical Cases with Particular Reference to the Arterial Phenomena of Aortic Regurgitation, Heart **10** 301, 1923

insufficiency. However, it remained for Smith, Miller and Graber²⁴ to demonstrate that the coronary flow was actually decreased in experimental aortic insufficiency in dogs, and that this decrease was caused by the lowering of the diastolic level. We have, then, definite proof that in aortic insufficiency there is a diminished blood supply to the heart muscle, satisfactory grounds for assuming that anoxemia of the myocardium may ensue.

We shall point out later that the greatest stumbling block in the way of acceptance of the "coronary" (ischemia) theory are the cases in which coronary obstruction—that is to say, ischemia—cannot be demonstrated. To account for these cases, the hypothesis of coronary spasm as the cause of angina was developed. It is now possible to show that most, practically all, patients with angina pectoris do have a diminished blood supply to the heart, since practically all patients with angina have either coronary disease or aortic insufficiency. In the one case the decreased flow is due to anatomic alterations in the coronary vessels, in the other it is due to physiologic changes resulting from the valvular lesion. The end-result in both conditions is the same—anoxemia of the myocardium. It is no longer necessary to assume that spasm of the coronaries takes place in angina, a hypothesis which rests on uncertain evidence and to which there are weighty objections.

The relative frequency of angina pectoris in cases of aortic insufficiency caused by syphilis as compared with the occurrence of angina in cases of rheumatic aortic insufficiency has been pointed out and should be discussed. We believe that this discrepancy can be explained. In the first place, the valvular disease differs in the two types of cases. In syphilitic aortic insufficiency the valvular lesion is "pure," that is to say, it is uncomplicated by the presence of aortic stenosis. In rheumatic aortic insufficiency, however, there is likely to be associated a more or less marked degree of stenosis, which tends to counterbalance the effects of the insufficiency. The result is that usually the insufficiency is more marked in the syphilitic cases as evidenced by the greater lowering of diastolic blood pressure, the higher pulse pressure, etc. In the second place, and probably of great importance, is the fact that many of the patients with syphilitic aortic insufficiency have, in addition to this lesion, narrowing or complete occlusion of the orifices of one or both coronary arteries. As either one of these lesions may lead to a certain amount of diminution of coronary flow, the combined effect of the two tends to cause a greater disturbance than is likely to occur in the average case of rheumatic aortic insufficiency.

²⁴ Smith, F. M., Miller, G. H., and Graber, V. C. The Relative Importance of the Systolic and Diastolic Blood Pressure in Maintaining the Coronary Circulation, *Arch. Int. Med.* **38**: 109 (July) 1926.

Syphilitic Aortitis—It is well, at this point, to discuss the relationship of syphilitic aortitis to angina pectoris. The frequent association of the two conditions has been considered important evidence in favor of the aortic theory, particularly since aortic involvement seemed to account for the cases not explained by the coronary theory. However, it is essential that the facts of the case be carefully examined. It is insufficient to state merely that syphilitic aortitis was present in a case of angina, it is important to know whether syphilitic aortitis alone existed, or whether this condition was complicated by the presence of other lesions, namely, aortic insufficiency or occlusion of the coronary ostia, so commonly found in syphilitic aortitis. For example, it has been stated by Lamb¹⁴ that angina pectoris occurred in 11.35 per cent of 613 cases of syphilitic aortitis collected from the literature, yet it is difficult to determine from the published data the exact extent of the lesions found at necropsy.

TABLE 3—*Angina Pectoris in Syphilitic Aortitis. Observations at Necropsies*

| Authors | Total | Aortic Insufficiency | Coronary Involvement | Combined Aortic Insufficiency and Coronary Disease |
|--|-------|----------------------|----------------------|--|
| Present series | 5 | 5 | 2 | 2 |
| Gallavardin <i>Les angines de poitrine</i> , ed 1, Paris, Masson & Cie, 1925 | 7 | 3 | 7 | 3 |
| Pauli <i>Ztschr f Kreislaufforsch</i> 19:169, 1927 | 6 | 2 | 6 | 2 |
| Curshmann quoted by Stadler <i>Die Klinik der Syphilitischen Aortenerkrankung</i> , Jena, Gustav Fischer, 1912 | 1 | | 1 | |
| Osler <i>Lancet</i> 1:697, 839 and 973, 1910, <i>M Chron</i> 44:11, 1906 | 5 | 3 | 3 | 2 |
| Mackenzie <i>Angina Pectoris</i> London, Oxford University Press, 1923 | 5 | 3 | 5 | 3 |
| Pincoffs <i>Tr Am A Phys</i> 42:54, 1927 | 10 | Not mentioned | 6 | |
| Thayer <i>Internat Clin</i> 1:1, 1923 | 9 | Not mentioned | 5 | |

We²⁵ previously reported twenty-six cases of uncomplicated syphilitic aortitis, proved by necropsy, and in not one instance was there a history of angina pectoris. In table 3, we have listed the information obtained from some of the data in the literature.

In every case in which detailed information is given, either aortic insufficiency or coronary disease, or a combination of the two, is present in cases of angina pectoris associated with syphilitic aortitis. This is apparently true, too, in case of angina associated with aneurism. Frankel⁸ called attention to the fact that angina occurred in patients with aneurism, particularly when there were arteriosclerotic changes in the region of the coronary vessels. Mackenzie¹² recorded an instance (case 20) in which the coronaries were sclerosed and stated that "I am therefore of the opinion that, when the pain in such cases (aneurism) is found in the region characteristic of angina, it is the heart trouble

25 Keefer, C. S., and Resnik, W. H. Paroxysmal Dyspnea as a Symptom of Syphilitic Aortitis. *Arch Int Med* 37:264 (Feb) 1926.

which induces the pain" Similarly, Graham Steele²⁶ stated that the coronary orifices were always involved in cases of angina associated with aneurism. In the two cases described by Osler²⁷ in which necropsy notes are available, coronary disease was present in one and aortic insufficiency in the other.

In view of these facts, we are led to the conclusion that uncomplicated syphilitic aortitis never causes angina pectoris. When angina occurs in a case of syphilitic aortitis, either coronary disease or aortic insufficiency is also present.

It is not difficult to understand why aortic involvement is actually present in most cases of angina. Reference to the previously given classification of the pathologic conditions associated with angina pectoris will make this clear. We repeat that practically all cases of angina are associated with either coronary disease or aortic insufficiency. When coronary sclerosis is present, there are practically always sclerotic changes in the aorta. When narrowing of the coronary ostia exists, the condition is actually caused by syphilitic or arteriosclerotic lesions in the aorta. On the other hand, when angina is associated with aortic insufficiency, the insufficiency is caused in most instances by syphilitic aortitis, and it was just the few remaining cases of rheumatic aortic insufficiency, in which aortic lesions are not necessarily found that Allbutt was unable to explain by the aortic theory²⁸. We see, therefore, that aortic involvement is purely coincidental in angina. It happens to cause or to be associated frequently with the lesions that are responsible for angina.

Miscellaneous Conditions (Associated with Angina)—Although coronary disease or aortic insufficiency or both are present in almost every instance of angina, there are exceptional cases associated with other conditions. It is true that angina has been reported in a wide

26 Steele, Graham. Intrathoracic Tumors and Aneurysms in their Clinical Aspect, *Lancet* **2** 1605 (Dec 9) 1911.

27 Osler, Sir William. Angina Pectoris as an Early Symptom in Aneurism of the Aorta, *M. Chron.* **44** 11, 1906.

28 We are aware of the recent reports concerning the presence of aortic lesions in acute rheumatic fever (Pappenheimer, A. M., and von Glahn, W. C. Studies in the Pathology of Rheumatic Fever, *Am. J. Path.* **3** 583 [Nov.] 1927). However, we do not feel that these observations affect our conclusions. Before one could admit any possible bearing of these lesions on the occurrence of angina in patients with rheumatic heart disease, one would have to show that the lesions were present in every case associated with angina, and that most, if not all, of the patients in whom the lesions were present suffered from angina. In none of the cases described by Pappenheimer and von Glahn was true angina present, nor have the aortic lesions been described in any case of which we are aware of a patient with rheumatic aortic insufficiency associated with angina on whom necropsy was performed.

variety of maladies, but a detailed discussion of all of these instances would be profitless. In many cases, what has been termed angina has not been true angina, in many other cases, accurate pathologic data are lacking or incomplete. Thus, angina has been reported in cases of myxedema (Osler,⁹ Means, White and Krantz²⁹ and Sturgis³⁰). In one case studied by Sturgis, there was a severe secondary anemia, and necropsy showed extensive coronary changes. It is difficult under these circumstances to estimate accurately the rôle of the hypothyroidism or of the subsequent influence of thyroid extract, although it is possible to speculate on the effect of increasing the circulatory minute volume and the work of the heart by increasing the metabolism. Cases of angina have been described in association with hyperthyroidism (Means, White and Krantz,²⁹ Sturgis³⁰ and Chvostek³¹). We, too, have seen a patient whose attacks of angina pectoris were closely related to periods of active hyperthyroidism. During remissions, the attacks disappeared. But the condition of the coronary arteries is unknown in all these cases, and further discussion should be deferred until more definite and complete information is obtained. The same must be said about the attacks of pain that sometimes occur in paroxysmal tachycardia (Mackenzie,¹² Gallavardin¹⁰ and Barnes and Willius³²). Here, again, it is interesting to speculate on the part played by changes in coronary circulation and in work of the heart (demand for oxygen), but the question must be left undecided until we have further evidence regarding the anatomic state of the coronary arteries, and the alterations in coronary flow. It should be emphasized that it is essential to differentiate between the patients who have paroxysmal tachycardia as a result of coronary occlusion and those who develop angina because of the tachycardia. Angina has also been found in cases of Addison's disease (Rowntree³³) and polycythemia vera (Kahn³⁴), but necropsy records are not available.

There are certain cases, however, from which one may draw more definite conclusions, and they are of considerable interest.

29 Means, J. C., White, P. D., and Krantz, I. C. Observations on the Heart in Myxedema with Special Reference to Dilatation and Angina Pectoris, Boston M. & S. J. **195** 455, 1926.

30 Sturgis, C. C. Angina Pectoris as a Complication in Myxedema and Exophthalmic Goitre, Boston M. & S. J. **195** 351, 1925.

31 Chvostek, F. Morbus Basedowi und die Hyperthyreosen, Berlin, Julius Springer, 1917, p. 73.

32 Barnes, A. R., and Willius, F. A. Cardiac Pain in Paroxysmal Tachycardia, Am. Heart J. **2** 490 (June) 1927.

33 Rowntree, L. Studies in Addison's Disease, Tr. A. Am. Phys. **39** 426, 1924.

34 Kahn, M. H. Etiologic Factors in Angina Pectoris, Am. J. M. Sc., **172** 195 (Aug.) 1926.

Anemia Herrick and Nuzum³⁵ made the important observation that angina is sometimes associated with anemia. Later, Herrick³⁵ recorded additional cases and collected the literature on the subject. Coombs³⁶ and Bullrich³⁷ made similar observations, and the cases may be discussed together. It was found that the severity of the angina was proportional to the degree of the anemia, as the condition of the blood improved the angina tended to disappear. In the few patients on whom necropsy was performed, sclerotic changes were found in the coronary arteries, and Bullrich suggested that the anemia acted by diminishing the nutrition of the myocardium, already impaired by coronary disease. Mackenzie,¹² Levine,³⁸ Conner³⁹ and we have also observed cases in which there appeared to be a definite connection between the severity of anemia and the onset of attacks of angina pectoris.

Another important contribution was made by Willius and Giffin⁴⁰ who recently reported a case of pernicious anemia with typical attacks of angina. At necropsy, the coronary vessels and the aorta were found to be normal. Cabot⁴¹ also briefly mentioned three similar cases.

Though these cases are few in number, they are of great importance since they demonstrate beyond question the rôle of diminished oxygen supply to the heart in causing angina pectoris.

Arteriovenous Fistula Attacks of angina have been described in a few instances of arteriovenous fistula, the angina disappearing following surgical closure of the fistula (Perthes⁴²). This observation is of interest in view of the work of Lewis and Drury,²³ and of Smith, Miller and Grabel,²⁴ who showed that in arteriovenous fistula a lowering of the diastolic blood pressure and a consequent diminution in coronary flow result. This work adds significance to the report of Osler⁴³ that sudden death has occurred in patients with arteriovenous fistula, no obvious cause being found at necropsy.

35 Herrick, J. B. On the Combination of Angina Pectoris and Severe Anemia, *Am Heart J* **2** 351 (April) 1927, also, *Tr A Am Phys* **42** 23, 1927.

36 Coombs, C. F. A Note on the Cardiac Symptoms of Pernicious Anemia, *Brit M J* **1** 185, 1926.

37 Bullrich, R. A. Influencia patogenica de los estados anemicos sobre la angina de pecho, *Semana med* **2** 1137, 1925, quoted from Herrick, *Am Heart J* **2** 351, 1927.

38 Levine, S. A. Discussion, *Tr A Am Phys* **42** 30, 1927.

39 Conner, L. A. Discussion, *Tr A Am Phys* **42** 29, 1927.

40 Willius, F. A., and Giffin, H. Z. The Anginal Syndrome in Pernicious Anemia, *Am J M Sc* **174** 30 (July) 1927.

41 Cabot, R. C. *Facts about the Heart*, ed 1, Philadelphia, W. B. Saunders Company, 1926.

42 Perthes, G. *Munchen med Wchnschr* **32** 1113 (Aug 8) 1924.

43 Osler, Sir William. Remarks on Arterio-Venous Aneurysm, *Lancet* **1** 949, 1915.

Pericarditis We shall discuss the question of pericarditis and angina pectoris, not because of any intrinsic interest in the subject, but because of certain significance that has been attached to it. Pawinski⁴⁴ described several cases of angina occurring in patients with pericarditis, and Allbutt referred to this paper in support of his view that the pain in coronary occlusion was due to the development of pericarditis. However, Pawinski's paper was written at a time when the clinical picture of acute coronary obstruction was not well recognized. While but few necropsy data are given in the report, it seems clear from the clinical description and course of five cases, that the diagnosis of coronary occlusion is highly probable. In other words, pericarditis was the result of the angina (coronary occlusion) and not the cause. Moreover, in three other cases, aortic insufficiency was present and the part played by the pericarditis in causing the angina is again rendered doubtful. We do not know of any cases in which the dependence of angina on pericarditis is beyond question.

Neusser⁷ stated that attacks of angina pectoris had been reported in a few patients with adherent pericardium. In some of these, pericardial adhesions had caused constriction of the coronary arteries, in others, however, the coronary arteries were apparently intact. But he did not give any further data about the presence or absence of other lesions such as valvular disease, without which the cases neither support nor refute the anoxemia theory.

Mitral Stenosis The infrequency of angina pectoris in patients with mitral stenosis has long been recognized, although rare cases have been reported (Levine,¹⁷ Mackenzie¹² and Nothnagel⁶). In some cases, necropsy was not performed, in others, aortic insufficiency or coronary disease was present, rendering the significance of the mitral disease doubtful. Sternberg⁴⁵ reported a case of interest. He found at necropsy that the left anterior descending coronary artery may be compressed between the left auricle and the pulmonary artery in certain cases of mitral stenosis. In view of this observation, he suggested that this obstruction of coronary flow might be the cause of anginal attacks in cases of mitral stenosis. Telia⁴⁶ offered a similar explanation in an apparently identical case. It is difficult to understand, however, how the coronary artery, under arterial pressure, could be seriously compromised.

44 Pawinski, J. Ueber den Einfluss der trockenen Pericarditis auf die Entstehung der Stenocardie und cardial Asthma, *Deutsches Arch f klin Med* **58** 565, 1896-1897.

45 Sternberg, M. Stenokardie bei Mitralfehlern, *Ztschr f klin Med* **97** 110, 1923.

46 Telia, L. Considerations sur le syndrome de l'angine de poitrine dans la stenose mitrale, *Arch d mal du coeur* **18** 531, 1925, abstr, *Am Heart J* **1** 386, 1926.

by pressure between structures ordinarily under considerably less tension. Without more data, it must be confessed that the validity of the explanation given is open to question.

There remain but few cases which may be considered possible examples of genuine angina pectoris and which do not fall into one of the groups described. Osler's case,⁹ in which lesions of the coronary arteries or aorta were absent, is open to question. One is impressed by the atypical features of the attacks of pain, and the relationship of the final attack to the death is doubtful, as chloroform had been administered during the attack. It has been demonstrated by Levy⁴⁷ that this substance is capable of causing sudden death by inducing ventricular fibrillation. Of all Gallavardin's patients in whom genuine angina was considered to be present, only one failed to show coronary disease or aortic insufficiency at necropsy. In this instance, "azotemic" nephritis was present, a condition frequently associated with severe anemia. It is not stated whether anemia was present in this patient, but without this information it is impossible to be certain that anoxemia of the heart was not present. Allbutt³ was able to collect but fifteen cases from the literature. However, one (case 13) was clearly an instance of coronary obstruction, and in four aortic insufficiency was present. In the others, the condition of the aortic valves or anemia are not mentioned. It is not only impossible to exclude anoxemia in some of these cases, but it is possible that the cases were not instances of genuine angina pectoris, but belonged rather to the group described by Gallavardin¹⁰ as being "para-dyspnoeic," and which he considers distinct from genuine angina.

In summarizing this section on the pathology of angina pectoris, we feel justified in stating that when the facts are complete, it is possible to demonstrate conditions capable of leading to anoxemia of the myocardium in practically every case. In the few remaining cases in which this is not apparently true, either the diagnosis is doubtful or the data are inadequate to exclude the possibility of anoxemia being present.

CRITICAL REVIEW OF PREVAILING THEORIES OF PATHOGENESIS OF ANGINA PECTORIS

There are, at present, three outstanding theories of the pathogenesis of angina pectoris which merit particular attention: (1) coronary theory, (2) aortic theory, (3) myocardial exhaustion theory.

1 *Disease of the Coronary Arteries*—It was natural that coronary disease should have been implicated early in the explanation of the mechanism of angina pectoris. Coronary obstruction, more or less complete, either by a sclerotic process in the course of the artery, or by

⁴⁷ Levy, A. G. The Exciting Causes of Ventricular Fibrillation in Animals Under Chloroform Anesthesia, *Heart* 4 319, 1912-1913.

occlusion of the mouth of a coronary artery through sclerosis or syphilitic involvement of the aorta, was so frequently found at autopsy in persons with the condition, that a connection seemed inevitable. This view first proposed by Jenner and Parry, and later brilliantly upheld by Potain and Huchard, has, nevertheless, been abandoned in its strict sense. Two important obstacles stood in the way of accepting this theory: (a) cases in which marked obstruction of the coronary arteries was found, in which angina pectoris had not been present during life; (b) cases of unquestionable angina pectoris in which the coronary arteries were found absolutely uninvolved at autopsy.

The first objection to the coronary theory, namely, that coronary obstruction can exist without angina pectoris being present, can no longer be considered valid. This objection was raised at a time when it was held that the coronary arteries were terminal arteries and did not have any appreciable anastomotic relationship with each other. Modern work has shown that this assumption is untrue. The work of Gross,⁴⁸ Spalteholz⁴⁹ and Oberhelman and LeCount⁵⁰ has demonstrated beyond a doubt that relatively rich communications may exist between the branches of the coronaries, the extent of the anastomosis usually increasing with the age of the patient. Moreover, it is a matter of common observation that particularly in syphilitic involvement of the aorta, the mouth of a coronary artery may be completely occluded without any evidence of myocardial infarction, that is to say without any evidence to show that the heart muscle supplied by the occluded artery had suffered any nutritional disturbance. These observations led to the view (Oberhelman and LeCount⁵⁰) that myocardial damage depends on (a) the rapidity with which the occlusion takes place—the slower the process the greater the opportunity for anastomosis to develop, (b) the richness of the preexistent anastomosis with the obstructed vessel. Even in the event of an acute obstruction, the connections with the occluded vessel may be so extensive that a serious diminution in the supply of blood to the area of the heart muscle supplied by the obstructed vessel need not develop. The recent work of Wearn⁵¹ has emphasized the importance of another avenue by which the myocardium may receive an adequate blood supply in spite of a coronary obstruction, namely, the Thebesian vessels.

48 Gross L. *The Blood Supply to the Heart, in Its Anatomical and Clinical Aspects*, ed 1, New York, Paul B Hoeber, 1921.

49 Spalteholz, W. *Die Arterien der Herz wand* Leipzig, 1924.

50 Oberhelman H A and LeCount, E R. *Variations in Anastomosis of Coronary Arteries and their Sequences*, J A M A 82 1321 (April 26) 1924.

51 Wearn, J T. *The Role of the Thebesian Vessels in the Circulation of the Heart*, J Exper Med 47 293 (Feb 1) 1928.

Another important factor of a different nature must be considered, namely, the sensitivity of the patient to pain (Libman⁵²) There is a condition in which association with pain is unquestioned, namely, acute coronary obstruction with myocardial infarction Yet even in this condition there may be a complete absence of pain It is not uncommon to find at autopsy old scars in the heart muscle, or even fresher infarcts, due to coronary obstruction in cases in which a history of pain was not elicited⁵³ Huchard⁴ and Gallavardin¹⁰ reported such instances, and attributed the absence of pain to the fact that pain could not arise from dead tissue We do not consider this explanation satisfactory Pain cannot be expected to arise from dead tissue, but this tissue must first pass through a stage of injury, when one does expect pain There can be but little doubt that it is the injury of the myocardium and not the actual death, that causes pain in cases in which there is a myocardial infarct We are more inclined to feel that in these instances of myocardial infarct pain is absent (*a*) either because the subject is relatively insensitive to pain,⁵⁴ (*b*) or because the infarction occurs so slowly, only a few fibers being injured at a time, that the resulting sensation is insufficient to arise in consciousness These cases are different from those (Herrick⁵⁵) in which following the obstruction with its accompanying pain, the angina disappears Here it is logical to assume that the infarction and subsequent scarring has thrown out of function, beyond doubt, the area of myocardium previously responsible for the pain

In view of the foregoing two considerations (*a*) instances in which adequate blood supply to the occluded territory is assured by compensatory anastomosis between the coronary arteries and further by the Thebesian vessels so that infarction does not take place, and (*b*)

52 Libman, E Observations on Sensitiveness to Pain, *Tr A Am Phys* **41** 305, 1926

53 We are unable to account for Gallavardin's (footnote 10) statement that in twenty-two of twenty-five cases of coronary obstruction with infarction pain was not present These figures give a totally different impression from those published in papers coming from this country (Herrick, J B Acute Obstruction of the Coronary Artery, *Northwest Med* **24** 593 [Dec 25] 1925, Clinical Features of Sudden Obstruction of the Coronary Arteries, *J A M A* **59** 2015 [Dec 7] 1912, Thrombosis of the Coronary Arteries, *ibid* **72** 387 [Feb 8] 1919 Wearn, J T Thrombosis of the Coronary Arteries with Infarction of the Heart *Am J M Sc* **165** 250 [Feb] 1923 Libman, E Some Observations on Thrombosis of the Coronary Arteries, *Tr A Am Phys* **34** 138, 1919 Hamman, L V The Symptoms of Coronary Occlusion, *Bull Johns Hopkins Hosp* **38** 273 [April] 1926)

54 This view is not far-fetched One is not astonished at observing a fatal hemorrhage or perforation from a large peptic ulcer which had hitherto remained absolutely symptomless, or which may be discovered as an unsuspected observation at autopsy

55 Herrick (footnote 53, first reference)

instances in which pain is probably not felt even when infarction does ensue either because of the patient's diminished sensitivity to pain, or because of the slowness of the process of infarction, it can no longer be held that coronary disease without angina pectoris is a valid argument against the theory that the coronary arteries are implicated in angina pectoris

There remain the cases of angina pectoris without organic coronary disease. These cases constitute a far more serious objection to the acceptance of an exclusive coronary theory. Albutt enumerated fifteen, and there are others in the literature. Some of these cases are unquestionably instances of genuine angina, but there is serious doubt about the accuracy of the diagnosis in others. For example Neusser⁵⁶ cited a case of Heine, one of so-called "plexus angina," in which at autopsy lesions (apparently, tuberculous lymph nodes) were found involving the phrenic and cardiac nerves and branches of the left vagus nerves. However, Neusser⁵⁷ himself admitted that the clinical history was not typical of angina pectoris as there was no characteristic pain on effort. It seems more likely that transient complete heart block was present. Neusser⁵⁷ also quoted a case of Wallenberg in which, following a stab wound there was "anguish in the cardiac region," together with a sensation as if the heart "stood still." Here again the history of the attacks is altogether atypical, and the diagnosis of angina pectoris is scarcely permissible. These cases are illustrative of many that have been inaccurately included under the category of angina pectoris merely because the patient has experienced distress in the region of the heart. They have served only to confuse the problem. It would be impossible to cover the entire literature of angina pectoris in an effort to sort out the cases of true angina from those in which the diagnosis is more or less questionable. One must agree with Gallavardin⁵⁸ that 'angina pectoris without coronary lesions does not mean much, if one does not define precisely with which syndrome one deals'.

Aside from the cases in which the history is sufficiently atypical that one has adequate grounds on which to question the accuracy of the diagnosis of angina pectoris, there are other examples in which it must be admitted that a close similarity with undoubted angina exists. We have shown, however, that practically all the patients have aortic insufficiency or some other lesion that may produce anoxemia of the myocardium.

56 Von Neusser, E. *Angina Pectoris*, New York, E. B. Treat & Co., 1909, p. 35, trans. into English by Andrew MacFarlane.

57 Von Neusser, E. *Angina Pectoris*, New York, E. B. Treat & Co., 1909, p. 41, trans. into English by Andrew MacFarlane.

58 Gallavardin, L. *Les angines de poitrine*, ed. 1, Paris, Masson & Cie., 1925, p. 128.

The coronary theory has been powerfully supported by the better appreciation of the clinical picture of acute coronary occlusion. This condition is so similar in many important respects to angina pectoris that a connection between the two has seemed unavoidable to many students of the subject. It is true that there are differences, which we shall analyze later, but the close correspondence in the essential features is inescapable. Allbutt³ has objected to this view, one of the reasons being that pain in coronary occlusion is due to the pericarditis that is sometimes associated with the condition, in other words, the pain has an altogether different origin from the pain of angina pectoris. This argument certainly has no basis. Aside from the fact that the type of pain is practically identical with the pain of angina pectoris, and quite different from the pain that one usually encounters in other forms of pericarditis, one needs only to point out that pericarditis is not at all a constant observation in cases of coronary occlusion with pain. For example, Wearn⁵⁹ found pericarditis in six of nineteen patients on whom autopsy was performed, of these, fifteen had acute coronary occlusion with pain as an outstanding symptom.

In spite of the objections that have been raised against the theory that organic disease of the coronary arteries (obstruction either in the course of the artery or at the mouth) is responsible for angina pectoris the idea of coronary involvement has not been abandoned. To account for the cases of angina without coronary disease, the conception of spasmodic constriction of the coronary arteries was evolved. This view, first advocated by Latham⁶⁰ and supported by Neusser⁷ and many others, among whom may be mentioned Gallavardin¹⁰ and Kohn,⁶¹ seems at first sight to be attractive. The attacks that characterize the condition are spasmodic, in the typical case they occur suddenly, they usually disappear quickly, and the agents that relieve the attacks, the nitrites for example, are those whose action diminishes vascular tone. However, there are difficulties in the way of acceptance of the hypothesis of "coronary spasm."

First of all, it is difficult to understand why this hypothetical spasm of the coronary arteries should occur only in certain types of cases, why, for example, it is excessively rare in rheumatic heart disease, particularly mitral stenosis, and, indeed, in all other types of heart disease except those associated with coronary disease or syphilitic aortitis. Secondly, it is difficult to understand how vasoconstriction could affect a coronary artery which was already altered by arterio-

⁵⁹ Wearn (footnote 53)

⁶⁰ Latham, P. M. *Diseases of the Heart* London, 1845, quoted from Kohn, H. *Med Klin* **22** 983, 1026 and 1063, 1926

⁶¹ Kohn, H. *Angina Pectoris, Aorten oder Koronarhypothese*, *Med Klin* **22** 983 (June 25) 1926, **22** 1026 (July 2) 1926, **22** 1063 (July 9) 1926

sclerosis Recognizing that vasoconstriction in an artery thickened and hardened by deposits of lime was a physiologic impossibility, Neusser⁷ proposed the idea that angina occurred only when the coronary arteries were slightly or moderately affected, when vasoconstriction could no longer take place, the attacks disappeared This conception is purely hypothetic, as there is no way of determining in life the degree of sclerosis of the coronary arteries and the possibility of vasoconstriction Moreover, it is contrary to experience, at least in the majority of cases, since one finds at autopsy more often than not a high grade of sclerosis in patients who, in life, had suffered from typical attacks of angina up to the time of death Case 6 of Gallavardin's series⁶² may be cited as a single example "the changes in the coronaries, atheromatous in nature involve the entire extent of the vessels, which, even at the periphery, roll under the finger like little calcified tubes." In the face of the foregoing observations, Gallavardin⁶³ went so far as to state that in acute coronary obstruction, the pain is not due to the actual obstruction, but rather to the coronary spasm that (he assumes) accompanies it Yet the symptomatology of acute coronary obstruction may occur in patients in whom at autopsy the coronary arteries do not differ much from those just described It is, moreover, exceedingly difficult to conceive of a spasm lasting for hours or even days, as does the pain in some cases of coronary obstruction, a spasm which is practically always unaffected by agents that are usually effective Finally, and most important, the idea of coronary spasm has been proposed and maintained in spite of almost directly contradictory facts of physiology It has yet to be proved that an effective coronary spasm can actually take place There has been little support for such an idea from experiments on mammals Recently, Anrep and Segall⁶⁴ have shown in experiments on the heart and lungs that the coronary arteries are actually affected by vasomotor nerves, the sympathetic nerves causing a dilatation, and the vagi, constriction Even their work has been questioned by Miller, Smith and Graber⁶⁵ who were led by their own experiments to the conclusion that diminution of coronary flow on stimulation of the vagi was purely the result of lowering of the heart rate A final decision must be held in abeyance If, however, for the sake of argu-

62 Gallavardin, L Les angines de poitrine, ed 1 Paris, Masson & Cie, 1925, p 143

63 Gallavardin, L Les angines de poitrine, ed 1 Paris, Masson & Cie, 1925, p 126

64 Anrep, G V and Segall H N The Regulation of the Coronary Circulation, *Heart* **13** 239 (Sept) 1926

65 Miller, H G Smith, F M, and Graber, V C The Influence of Changes in the Cardiac Rate and Irregular Action of the Heart on the Coronary Circulation, *Am Heart J* **2** 479 (June) 1927

ment, one does assume the possibility of vasoconstriction through stimulation of the vagi, but little support is given the coronary spasm theory in angina pectoris. Anrep and Segall⁶⁴ have shown that when the vagus is stimulated, slowing of the heart and diminution of coronary flow do not go hand in hand. When mild stimulation of the vagus is employed, slowing of the heart may occur without any decrease in coronary flow (that is, without vasoconstriction). The clinical application of their important results is that if vasoconstriction does take place, a slowing of the heart rate must be present. The assumption of vasoconstriction in angina pectoris falls to the ground, then, since there are not any characteristic changes in the heart rate during an attack of angina. The rate is usually unaltered, sometimes it is slightly decreased, and sometimes it is slightly increased. But there is no constant decrease, which is a necessary prerequisite for the acceptance of diminished coronary flow due to vagal stimulation, whether Anrep and Segall or Miller, Smith and Graber be ultimately proved correct. There remains, of course, the possibility that the results of the animal experiments do not necessarily apply to conditions in the human. For the present this is a gratuitous assumption. Together with the other facts at hand, these experimental results remain a most serious obstacle to the idea of coronary spasm in angina pectoris.

One would expect, if coronary spasm were the actual cause of angina pectoris, to find fairly frequent examples of myocardial infarct without organic obstruction of the coronary arteries. Occasionally one does see examples of healed infarct in which complete obstruction of the corresponding branch of the coronary artery does not exist. But these cases can be logically explained on the basis of recanalization of the previously existent thrombus. In addition, one may see areas of patchy necrosis in an area of muscle supplied by a markedly sclerotic coronary artery, which is, however, patent (e, g, cases 4, 6 and 8 of Gallavardin's series). This necrosis is, in all likelihood, due to the gradual death of small groups of muscle fibers caused by impaired coronary flow, rather than to sudden death resulting from complete obstruction. Gruber and Lanz⁶⁶ reported a case of infarct of the heart in a young soldier who had, in life, suffered from epileptiform attacks. The coronary arteries were apparently normal and there was not any obvious obstruction. The infarct was thought to be due to coronary spasm, and the epileptiform attacks to spasm of the cerebral vessels. Although the clinical history was not that of angina pectoris, the observations at autopsy apparently support the idea of coronary spasm. However, we do not feel that we

⁶⁶ Gruber, G. B., and Lanz, H. F. Ischämische Herzmuskelnekrose bei einem Epileptiker nach Tod im Anfall, *Arch. f. Psychiat.* **61** 98 (Sept.) 1919-1920.

are too conservative when we suggest that such a conclusion be accepted with the greatest caution. If coronary spasm can give rise to the development of myocardial infarct, it becomes surprising that such cases are not more frequent. Yet they must be of the greatest rarity—so rare that one cannot help entertaining a certain degree of skepticism concerning them, particularly when one recalls the admonition of Benson⁶⁷ that the arterial occlusion may be overlooked unless special care is used in opening the coronaries.

A modification of the coronary theory has been suggested by Danielopolu,⁶⁸ who considers angina to be due to disproportion between coronary flow and work of the heart. That is to say, coronary insufficiency may lead to angina pectoris in a normal heart with normal coronary arteries, if the demands on the heart are great enough, correspondingly lesser demands will bring on angina when the coronary arteries are diseased. Even this author invokes spasm as an explanation of angina under some circumstances. This view is satisfactory as an explanation of the cases with actual coronary disease, however, Danielopolu does not offer convincing evidence that such a coronary insufficiency is present when the coronary arteries are normal.

We may summarize this discussion by stating that, in spite of extensive pathologic evidence, it is not possible to accept a theory which maintains that organic coronary disease is present in every case of angina pectoris. Nor is it possible to accept, without serious question, the hypothesis of vasoconstriction to explain those cases of angina without coronary obstruction.

2 Disease of the Aorta—This theory is usually identified with the names of Allbutt and Vaquez, and more recently of Wenkebach also. Its chief support rests on the finding of involvement of the aorta in practically all cases of angina pectoris. This comes from the fact that practically all patients with angina have either arteriosclerosis or syphilitic aortitis. But the arguments that have been directed against the coronary theory are applicable to the aortic theory as well. (a) There are cases of angina pectoris without demonstrable disease of the aorta. Allbutt himself confessed that he was puzzled by the cases of aortic insufficiency of rheumatic origin in which disease of the aorta could not be discerned. Jamison and Hauser⁶⁹ reported a case of angina in a boy of 18 years, the autopsy revealed coronary disease but

67 Benson, R. L. The Present Status of Coronary Arterial Disease, *Arch Path* **2** 876 (Dec) 1926.

68 Danielopolu, D. The Pathology and Surgical Treatment of Angina Pectoris, *Brit M J* **2** 553 (Sept 27) 1924.

69 Jamison, S. C., and Hauser, G. H. Angina Pectoris in a Youth of Eighteen, *J A M A* **85** 1389 (Oct 31) 1925.

no involvement of the aorta (b) Extensive disease of the aorta may be present without the occurrence of angina. One need only think of the frequency of aneurisms in this region, and the comparative rarity of association of angina pectoris. We call attention to a previous study²⁵ in which a series of twenty-six patients with uncomplicated cases of syphilitic aortitis (proved by autopsy) were found to have been free from both paroxysmal dyspnea and angina pectoris.

To us the most serious objection to the aortic theory is that it does not supply an adequate explanation for the sudden death. It is remarkable that comparatively little attention has been paid to this striking deficiency in the theory. It is true that "vagal inhibition" was proposed by Allbutt as the cause of death in a paroxysm of pain. This explanation may have appeared logical at the time it was first suggested, it can no longer be accepted without grave doubt. Lewis⁷⁰ has justly stated "to accuse the vagus when unexpected syncope terminates life, in the absence of clear evidence of its responsibility is unjustifiable."

If one starts with the assumption that the train of symptoms in angina pectoris, which frequently ends in sudden death, is inaugurated by stimulation of the nerve endings in the aorta, then sudden death can occur only as a result of reflex stimulation through the vagus or sympathetic nerves. We are not aware of any evidence that stimulation of the sympathetic nerves may cause sudden death. The proved cases of standstill of the whole heart caused by vagal stimulation are rare,⁷¹ and the instances in which ventricular standstill has occurred have been almost entirely in cases with some degree of preexistent block. This is certainly not true in most cases of angina pectoris. One may also ask why there are not any evidences of vagal stimulation during severe attacks of angina that do not lead to sudden death. One would expect to find in these cases definite slowing of the heart rate and probably varying degrees of auriculoventricular block, which is not the case. If one asks further why involvement of the aorta without cardiac damage (the coronary arteries being intact and no aortic insufficiency being present) is not associated with sudden death, the answer is given that sudden death depends on the condition of the heart, a healthy heart withstands the vagal attack. If, however, the question depends purely on the condition of the myocardium, it is strange that sudden death is of the utmost rarity in a combination such as syphilitic aortitis and mitral stenosis, for example, even when the heart shows signs of being seriously damaged. In the study previously mentioned²⁵ we did not find cases of sudden death in instances of syphilitic aortitis associated

70 Lewis, Sir T. The Mechanism and Graphic Registration of the Heart Beat, ed 3, London, Shaw & Sons, Ltd, 1925, p 433

71 Lewis, Sir T. The Mechanism and Graphic Registration of the Heart Beat, ed 3, London, Shaw & Sons Ltd, 1925, p 418

with hypertension and myocardial failure. Finally, as we shall show later, the best evidence points to the sudden death being due to ventricular fibrillation. So far as we know, vagal stimulation does not play an important part in the production of ventricular fibrillation. Experimentally, Drury⁷² was not able to detect any influence of vagal stimulation on the refractory period of the ventricle. If, as seems likely, ventricular fibrillation depends on the same mechanism as does auricular fibrillation, namely, the development of a circus movement, it is practically essential that changes in the refractory period of the muscle occur.

In the face of these facts, we cannot see any reason for attributing angina not only exclusively, but even occasionally, to lesions of the aorta. The aortic theory leaves unexplained the cases in which disease of the aorta cannot be discovered, it does not afford a logical explanation for the mechanism of sudden death which is so closely bound with the entire problem of angina, and it rests solely on the fact that most cases of angina are found to have lesions of the aorta, which, we have shown, is purely a coincidence.

3 Exhaustion of the Myocardium—Of Mackenzie's twenty-two patients on whom autopsy was performed, eighteen had definite involvement of the coronary arteries, of these, three had an associated aortic insufficiency, two had aortic stenosis and one had an aneurysm. Two had myocardial changes (presumably due to coronary disease although this is not definitely stated) and two had combined aortic, mitral and tricuspid disease of rheumatic origin. In the latter two patients there apparently was not any coronary disease. Mackenzie was convinced of the importance of the coronary arteries in angina pectoris, but being unable to explain the cases in which the coronaries were uninvolved, he resorted to the conception of "myocardial exhaustion," usually due to deficient blood supply, occasionally to exhaustion from other causes. He confessed that he was puzzled by the frequency of angina pectoris in cases of aortic insufficiency.

One gathers the impression that Mackenzie was essentially a "coronarian" and that the idea of "myocardial exhaustion" was one which was designed to cover those cases in which there was not any coronary disease. In view of the indefiniteness of the term "exhaustion," it is rather difficult to advance arguments for or against this hypothesis. It is not acceptable, however, for it leaves unexplained the irregularity in the occurrence of angina pectoris in various types of heart disease with exhausted heart muscle. It does not account for the frequency of

72 Drury, A. N. The Influence of Vagal Stimulation upon the Force of Contraction and the Refractory Period of the Ventricular Muscle in the Dog's Heart, *Heart* **10** 405 (Oct. 23) 1923.

angina in cases with coronary disease or aortic insufficiency or the rarity in cases with mitral stenosis, for example. Indeed, it is well known that when the myocardium is most exhausted, that is, when the evidences of congestive failure are most marked, the symptoms of angina tend to disappear, even in persons who have previously been subject to the condition. It is rather when the myocardium has a relatively good reserve, as manifested by the freedom from dyspnea, that the anginal symptoms are most striking. The hypothesis does not explain why all patients who ultimately die of heart failure, exhaustion of the myocardium, do not sometime in their career, suffer from angina.

In summary, it may be stated that all three of the theories as they stand today are inadequate. On the other hand, we have demonstrated before that practically all cases of "true" angina pectoris have lesions that may produce anoxemia of the myocardium, and it remains to show how anoxemia may bring about the manifestations that characterize angina pectoris.

CAUSE OF PAIN IN ANGINA PECTORIS

The striking similarity between angina pectoris and intermittent claudication has long been noted. In both instances the pain is brought on by effort, it is cramplike in character and rapidly relieved by rest. In intermittent claudication there is not any question about the cause of the pain—it is due to diminished blood supply to the muscles.

The experimental work of MacWilliam and Webster⁷³ is important in explaining certain characteristics of the pain in skeletal muscle. They found that when the blood supply to the arm is shut off by constriction, pain is not caused even at the end of twenty minutes, provided the muscles remain quiet. When, however, the ischemic arm is made to contract, fatigue is brought on much more quickly than it is in the normal arm, and at the fatigue point, there is severe pain. Moreover, pain can be elicited even before the fatigue point is reached, at a time when the contractile power of the muscle is still good. This latter fact is of importance, since it is at least a partial answer to the objection that may be raised, namely, that heart muscle cannot be fatigued. It demonstrates that whether or not there is any relationship between pain and fatigue under the circumstances of a muscle contracting when its oxygen supply is inadequate, pain is the earlier manifestation. In view of the close correspondence of these results with the clinical facts of angina pectoris, these authors suggest that processes of essentially the same nature are responsible for the pain in the latter condition.

⁷³ MacWilliam, J. A., and Webster, W. J. Some Application of Physiology to Medicine. I. Sensory Phenomena Associated with Defective Blood Supply to Working Muscles, *Brit. M. J.* **1**: 51 (Jan. 13) 1923.

Even more convincing evidence is afforded by the natural experiment of acute coronary obstruction a condition characterized by one outstanding circumstance the production of a sudden acute anoxemia of the myocardium. It is scarcely necessary to call attention to the similarity of this pain to that of angina pectoris, attested from the fact that acute coronary occlusion was long called status anginosus. Whatever difference exists between the two conditions is explainable by the persistence of anoxemia in acute coronary obstruction. This condition bears the same relation to angina pectoris that an acute and complete obstruction of the femoral artery bears to intermittent claudication.

Unfortunately the nature of the problem makes it impossible at present to obtain more direct evidence with regard to the question of pain by means of controlled experiments. When one considers, however that a picture analogous to that of angina pectoris is produced in skeletal muscle by a diminished blood supply, and also that "status anginosus" is caused clinically by acute coronary obstruction, it seems to us that the evidence is strong that anoxemia of the heart muscle can cause the pain of angina pectoris. This conclusion attains added significance in view of the pathologic data demonstrating in practically every authentic case of angina a lesion that gives rise to anoxemia of the myocardium. Not only, then do we have a highly suggestive and reasonable explanation for the pain in angina but we are not aware of any actual facts that speak so directly for distention of a diseased aorta as a possible cause of anginal pain. One would expect such a pain to arise in many instances of tabetic crises, for example, or in attacks of lead colic, in which a sudden acute hypertension occurs, presumably causing at least as much distention of the aortic wall as will occur in the ordinary muscular exercise that brings on pain in angina pectoris. This is not the case. Nor is there any actual support for the belief that an "exhausted" myocardium can cause pain which simulates closely the pain of angina.

It would not serve any useful purpose to speculate much on the actual mechanism of pain stimulation in the presence of anoxemia of the myocardium. Nor is it pertinent to this discussion to comment on the nervous pathways of the sensory stimuli from the heart. It is well to call to mind again, however, a point which we have already mentioned namely the probable variation in sensitivity to pain in different persons, as this may account for the occurrence of marked coronary disease even with complete obstruction in patients who may ultimately die of the disease without ever having experienced pain during life.

CAUSE OF SUDDEN DEATH IN ANGINA PECTORIS

One of the remarkable features of angina pectoris is the frequency of sudden death. This has been commented on since the time of Heberden. Of Mackenzie's 284 fatal cases 120 terminated suddenly

As the figure 284 includes many instances of "secondary" angina, that is to say, cases which were not true angina at all, the percentage of sudden deaths among the cases of true angina is higher than would appear from the figures. In Windler's⁷⁴ group of twenty-eight patients, sixteen died suddenly. In a group of twenty-three fatal cases studied by Willius,⁷⁵ in eighteen, or 76 per cent, death was sudden. In our own group of fifteen fatal cases, eleven ended by sudden death. It would seem that about 60 to 75 per cent of the patients with angina die suddenly.

It may be well to approach the topic from another angle, and to inquire in what forms of heart disease sudden death comparable to the death in many cases of angina is likely to occur. The frequency in coronary disease is well known. Thus, in 200 patients with more or less extensive coronary disease, 160, or 80 per cent, died suddenly (Benson and Hunter⁷⁶). In another group, 49 per cent of the patients with arteriosclerotic heart disease died suddenly (Willius). It is probable that approximately the same percentage of instances of sudden death would be found in other large series of cases of marked coronary disease. The other condition in which sudden death is a striking occurrence is aortic insufficiency, particularly of syphilitic origin. This is a well known clinical fact. In a group of twenty-one fatal cases of syphilitic aortic insufficiency that we have observed in sixteen, or 76 per cent, death was sudden, of these, in eight there was occlusion of one of the coronary ostia. Stadler⁷⁷ reported sudden death in twenty-three of his fifty-two patients with aortic insufficiency, there was encroachment of the coronary orifices in twenty-two instances, a remarkably high percentage. While sudden death may occur when the coronary arteries are involved, it is much more frequent when aortic insufficiency is present as well. Sudden death is not infrequent in rheumatic aortic insufficiency, and Moore⁷⁸ stated that "such cases generally terminate in sudden death and, of all causes of transition from what seems fair health to immediate death, aortic valvular disease is the most frequent."

We have not attempted to gather more statistics bearing on this subject, as we believe the conclusions are sufficiently well recognized

⁷⁴ Windler, quoted by Mackenzie (footnote 12, p. 114)

⁷⁵ Willius, F. A. Mode of Death in Various Types of Heart Disease, *Am J M Sc* **171** 480, 1926

⁷⁶ Benson, R. L., and Hunter, W. C. The Pathology of Coronary Arterial Disease, *Northwest Med* **24** 606 (Dec.) 1925

⁷⁷ Stadler, E. Die Klinik der syphilitischen Aortenerkrankung, Jena, Gustav Fischer, 1912

⁷⁸ Moore, Norman. Rheumatic Fever and Valvular Disease, *Lancet* **1** 1159 (April 24) 1909, **1** 1227 (May 1) 1909, **1** 1297 (May 8) 1909

to be beyond serious dispute. It is seen then, that sudden death occurs in exactly those conditions with which angina pectoris is most often associated—coronary disease and aortic insufficiency, especially of syphilitic origin. There is apparently some fundamental relationship between the characteristic pain of angina pectoris and the phenomenon of sudden death.

To MacWilliam⁷⁹ belongs the credit of having first suggested ventricular fibrillation as the probable mechanism by which sudden death occurs in heart disease. He was led to this conclusion from the observation that in experimental work on animals sudden death always resulted at the onset of this rhythm—it never took place by sudden standstill of the heart. He also noted that ventricular fibrillation was particularly prone to occur when the ventricles were rendered susceptible by a poor blood supply or by the long duration of the experiment. Resnik⁸⁰ also pointed out the marked tendency for ventricular fibrillation to develop when dogs were subjected to breathing mixtures of low oxygen pressure. Under these conditions the abnormal rhythm sometimes occurred spontaneously, more frequently it was caused by some stimulus, such as slight handling of the ventricle—a procedure insufficient ordinarily to cause such an effect in a well-oxygenated heart.

Further important experimental evidence is available in the work of Lewis⁸¹ and of Smith⁸² on experimental ligation of the coronary arteries. They showed that sudden death following the ligation was due to ventricular fibrillation, often preceded by ventricular tachycardia. In the light of these experiments considerable significance is attached to the observations of Robinson and Hermann⁸³ who reported clinical cases of ventricular tachycardia due to coronary occlusion.

When we sum up these data we find that not only does angina pectoris terminate suddenly in a high percentage of cases but that sudden death in heart disease occurs in just those cases that have lesions

79 MacWilliam I. A. Cardiac Failure and Sudden Death. *Brit M J* **1** 6 (Jan 5) 1889. Some Applications of Physiology to Medicine. II. Ventricular Fibrillation and Sudden Death. *ibid* **2** 215 (Aug 11) 1923.

80 Resnik W. H. Observations on the Effect of Anoxemia on the Heart. I. Auricular-Ventricular Conduction, *J Clin Investigation* **2** 93 1925. II. Intraventricular Conductions. *ibid* **2** 117, 1925. III. Changes in the Auricles, with Particular Reference to the Relationship Between Anoxemia and Auricular Fibrillation. *ibid* **2** 125, 1925.

81 Lewis, T. The Experimental Production of Paroxysmal Tachycardia and the Effect of Ligation of the Coronary Arteries, *Heart* **1** 98 1908.

82 Smith, F. M. The Ligation of Coronary Arteries with Electrocardiographic Study. *Arch Int Med* **22** 8 (July) 1918, Electrocardiographic Changes Following Occlusion of the Left Coronary Artery, *ibid* **32** 497 (Oct) 1923.

83 Robinson G. C. and Hermann G. Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion. *Heart* **8** 59 1921.

commonly associated with angina. We find also that the weight of experimental evidence supports the view that sudden death is practically always due to ventricular fibrillation, and that this rhythm is particularly likely to develop under conditions that produce anoxemia of the myocardium. Finally, there is proof that ventricular tachycardia, a forerunner of fibrillation, is frequently due to coronary obstruction in clinical cases.

Not uncommonly sudden death occurs in patients who have apparently never suffered pain. We have already referred to the frequency of such an event in patients with syphilitic aortic insufficiency or with more or less severe coronary obstruction. It is reasonable to assume that the state of anoxemia dependent on these lesions has predisposed the ventricles to fibrillation, as it does experimentally. This rhythm may then develop spontaneously, or it may be set off by some stimulus. It is possible that an extrasystole may act in such a manner, just as a properly timed shock may experimentally determine the onset of auricular fibrillation (Lewis). It is, of course, practically impossible to determine with certainty what the actual final stimulus is that causes the appearance of ventricular fibrillation in the clinical case. It would seem, however, that some condition producing anoxemia of the ventricle is an almost necessary predisposing factor.

If we accept the views that anoxemia of the heart muscle produces the pain of angina pectoris, and that ventricular fibrillation, caused fundamentally by anoxemia, is the cause of sudden death, it becomes clear why sudden death is so common in angina and why this frequent outcome is so inseparably bound with true angina. The pain and the sudden death are both expressions of the same underlying cause. One may almost state that the termination of the condition depends on the accidental development of circumstances that favor the appearance of ventricular fibrillation. Once the ventricle has been rendered susceptible by anoxemia, this rhythm may appear at any time, usually after paroxysms of pain have occurred over varying periods, sometimes even before any pain has ever been caused. Its appearance is synonymous with practically instantaneous death.

ANGINA PECTORIS AND CORONARY OBSTRUCTION

We have already intimated that the close similarity between the clinical aspects of angina pectoris and acute coronary occlusion constitutes evidence of great importance in establishing the coronary (anoxemia) theory. Yet the fact that there are certain differences in these conditions has been used by Allbutt⁸³ to discredit the strength of the argument. Lambert⁸⁴ has also emphasized the differences between

84 Lambert, Alexander. Cardiac Pain. *Am Heart J* 2 18, 1926.

coronary disease and angina pectoris, and they can best be shown by the following outline

| <i>Coronary Disease</i> | <i>Angina Pectoris</i> |
|-----------------------------|---|
| Epigastric pain more common | Epigastric pain less common |
| Dyspnea present | Dyspnea absent |
| Arrhythmias frequent | Arrhythmias absent |
| Frequency of râles in lungs | Lung signs absent |
| Pain is of long duration | Pain is of short duration |
| Nitrites do not give relief | Pain relieved by nitrites |
| Attacks may occur at night | Attacks rare at night, except late in disease |

It is obvious that what is called "coronary disease" by Lambert is actually acute coronary obstruction. That being the case, one may add other differential points: fever, leukocytosis, pericarditis, emboli in distant organs, low blood pressure, acute pulmonary edema and urinary suppression—all these occurring in acute coronary occlusion and all absent in angina pectoris. However, none of these so-called differential points holds in coronary disease without complete occlusion, and it is not difficult to explain their presence when acute and complete occlusion does take place.

The position and radiation of the pain do not differ fundamentally in the two conditions, usually being exactly the same. It does seem true that epigastric pain is relatively more common when acute obstruction develops, but epigastric pain in angina pectoris is far from uncommon, and such a relative difference can hardly be considered of serious import in distinguishing between "coronary disease" and angina pectoris. The occurrence of dyspnea, arrhythmias and signs of congestion in the lungs are simply and logically attributed to the fact that in acute coronary obstruction, myocardial infarction takes place, a greater or lesser part of the myocardium is thrown completely out of function. It is not surprising, under these circumstances, if changes in rhythm and signs of myocardial failure (so-called congestive type) arise. It is characteristic of angina pectoris that when pain develops, the patient stops short and usually maintains absolute quiet until the paroxysm has disappeared. Such absolute quiet is not often present in cases of acute coronary obstruction and with good reason. The patient with angina is brought to a halt by his pain since he has learned from experience that the less he moves the more rapidly will his pain disappear. The patient overcome by coronary occlusion is not faced by any such happy solution of his problems. As in typical angina, anoxemia of the myocardium develops. However, it is not due to a transient inability on the part of the heart muscle to receive an adequate supply of oxygen. It is due to a lesion which cuts off the oxygen supply permanently. Not only, then, is the pain more severe, but it persists

The most profound quiet will not cause its underlying cause to disappear. Is it to be wondered at that such a patient does become restless and toss about? This is what will occur in any condition associated with excruciating pain when quiet will not relieve the pain. It becomes apparent, too, why nitrites will not affect such a pain. It does so in angina pectoris by lowering the blood pressure and possibly dilating the coronary arteries, thus doing away with the condition of relative anoxemia of the heart—diminishing the demand for oxygen, and at the same time increasing the supply. These effects can have little or no influence on a type of anoxemia caused by actual obstruction of the artery. The anoxemia is no longer relative and transient, it is permanent and absolute (disregarding compensatory anastomoses that may later develop). The frequency of occurrence of acute coronary occlusion at night is purely a question of chance. An obstruction is just as likely to form during the night as during the day. The usual absence of nocturnal pain in angina is conditioned solely by the fact that the patient is at rest, he does not undertake any effort sufficient to bring on pain. It is unnecessary to enter into a detailed explanation of the other manifestations of acute coronary occlusion—fever, leukocytosis, pericarditis, etc. These symptoms can all be explained as being the result of the presence of dead tissue in the myocardium, and the effects of the sudden devitalization of a greater or lesser part of the myocardium.

An analysis of the apparent differences between "coronary disease" and angina pectoris reveals that these differences are entirely dependent on the differences in degree of anoxemia of the heart muscle in the two conditions. We repeat that in angina pectoris the anoxemia is relative and transient. It disappears when the cause of the anoxemia, increased work of the heart, disappears. In acute coronary occlusion, the anoxemia is absolute and permanent. The blood supply is shut off, and effort is no longer necessary to bring on anoxemia. Acute coronary obstruction is prolonged angina pectoris. It is, in fact, exactly what it used to be termed before the clinical picture of coronary occlusion was well understood, status anginosus. It is, however, something more than a severe, prolonged attack of angina, for the simple reason that the permanency and degree of the anoxemia introduce another factor, myocardial infarction, and the events that depend on this development.

ANGINA PECTORIS AND OTHER TYPES OF CARDIAC PAIN

We have stated before that the term "angina pectoris" should be applied only to the condition that corresponds to the one described by Heberden, characterized by a more or less typical pain and by the likelihood of termination by sudden death. We have insisted on the essentiality of this second feature, because we believe the evidence is

sufficiently strong to attribute its occurrence to the same underlying cause that brings on the pain, anoxemia of the heart muscle

There is not any doubt that there are other types of cardiac pain which closely simulate "true" angina pectoris. One may add that in some instances the pain may be indistinguishable clinically from the pain of the condition described by Heberden, at least by our available methods. Yet these pains do not merit the name "angina pectoris" since they do not have the same cause. They do not depend on a disturbance of function that may lead to sudden death. The fact that the pain may closely resemble that of angina pectoris need not lead us astray in our formulation of a conception of the pathogenesis of angina. Is it unreasonable to assume that the stimulus that gives rise to the pain in these cases, irrespective of the cause of the pain, reaches the same nervous paths that are brought into play in Heberden's angina, and hence produces pain of essentially the same distribution? Yet it must not be assumed that pain occurring in a certain region of the chest and radiating in a characteristic way is necessarily synonymous with the condition called angina pectoris.

We may illustrate our meaning by an analogy. The pain of duodenal ulcer has certain well defined features that are well known and need not be enumerated. It is a matter of common experience that identical symptoms may be caused by conditions other than duodenal ulcer. To carry the analogy further, it can be stated that one great difference between these conditions and duodenal ulcer is that in the former there is no possibility of the occurrence of certain events that may distinguish the latter, namely, the occurrence of hemorrhage or perforation. In spite of the similarity in symptomatology, the pathologic basis for the full development of the clinical picture of duodenal ulcer is not found in these other conditions. No one considers them the same in spite of the clinical resemblance.

We do not wish to enter into a discussion of the differential diagnosis of angina pectoris. This has been ably done before. We do wish to emphasize that the condition described by Heberden has a definite and single cause, anoxemia of the heart muscle. The problem of angina pectoris is not to determine what may be its cause⁸⁵. It is to determine, whether, in a given case, angina pectoris is actually present. When the diagnosis is reached, there should be the implication that anoxemia of the heart muscle is present and that sudden death may ensue. This statement is not a mere play on words. It is the attempt to define the nature of the malady clearly described by Heberden. If we substitute "anoxemia" for "coronary disease," the aphorism of Huchard is true

85 We do not mean that it is unimportant to determine the etiology of the lesion producing anoxemia of the myocardium. If this is found to be syphilis, for example, striking therapeutic results may be obtained by appropriate measures.

"There is only one angina pectoris, the angina pectoris due to anoxemia of the myocardium. All others are false."

CONSIDERATION OF CERTAIN PROBLEMS CONCERNED WITH THE ANOXEMIA THEORY OF ANGINA PECTORIS

A certain number of questions come to mind with regard to the relation of anoxemia to angina pectoris, some of which can be answered, and others of which must be left to future solution. Why, for example, should anoxemia ever occur in the heart muscle in a case of coronary disease, if there are anastomoses between the coronary arteries, and if the Thebesian vessels can nourish the heart muscle even when the coronary arteries are completely obstructed? It is true that the myocardium may not suffer any apparent injury in the presence of a marked occlusion of one or even both coronary arteries. But the fact remains that myocardial injury does occur in many instances, and the problem is to determine not whether anoxemia of the myocardium may occur, but rather under what circumstances it does occur. The question has been well answered and summarized by Oberhelman and LeCount to whose work we have already referred. Infarction following coronary obstruction depends on the rapidity of the vascular occlusion and the richness of the preexistent anastomoses. In addition, Wearn's work has showed that a third important factor is the extent to which the Thebesian vessels may take up the burden of nourishing the myocardium. We have the two extremes: in the one case, complete compensation for an obstruction of the coronary artery, so that the patient does not suffer any symptom and the heart muscle does not undergo any change as a result of the vascular occlusion, in the other case, myocardial infarction takes place. Between these two extremes lie the various gradations of symptoms and pathologic damage that may be present in angina.

A much more difficult problem is to determine why angina pectoris develops in such a relatively small percentage of the patients with aortic insufficiency, all of whom have a lowering of the diastolic pressure, and hence, presumably, a reduction of the coronary flow. Does the reduction of the coronary flow necessarily mean a reduction of blood supply to the myocardium? The rôle of the Thebesian vessels under these circumstances is not known, and it is possible that the extent to which these vessels may compensate for the reduced coronary flow may play some part in determining whether angina develops. One fact of clinical interest tends to demonstrate that aortic insufficiency does act by diminishing the coronary blood supply. Angina pectoris is much more common in syphilitic aortitis when both aortic insufficiency and occlusion of a coronary ostium are present, than when the latter lesion alone exists. In other words, the valvular lesion adds something to favor the development of angina, and it is logical to assume that this factor is the

diminution in blood supply through the coronary arteries. In addition to the question of the rôle of the Thebesian vessels, a second factor of considerable importance in this connection is the probable variation in the capacity of the heart muscle to resist the effect of anoxemia (to incur an "oxygen debt"). These two factors, the degree of compensation through the Thebesian vessels, and the individual variation in the myocardial tissue to withstand anoxemia, in addition, of course, to the extent of the valvular lesion, are probably important in determining whether or not angina appears in a case of aortic insufficiency. However, at the present, there is no definite answer to this problem, and the same holds true for the question of angina in pernicious anemia. What we have attempted to do is to show that in every case of genuine angina pectoris there is a lesion that may produce anoxemia of the myocardium, and that anoxemia of the myocardium may account for all the characteristic manifestations of angina, conversely, angina does not develop in the absence of anoxemia, and theories which assume some other derangement of function do not explain the characteristic features of angina. We do not yet know under just what circumstances anoxemia will affect the myocardium so that angina will appear, or by what mechanism anoxemia calls forth a paroxysm of pain. But these uncertainties do not differ materially from innumerable similar ones in clinical medicine, even in conditions that are well understood. It is generally agreed that "mountain sickness" is caused by anoxemia, yet symptoms appear in one person, and fail to appear in another, when both are subjected to the same degree of anoxemia (lowered oxygen tension). To say that the extent of the symptoms depends on the completeness of compensation for the anoxemia is no more than saying the same about the appearance of angina pectoris when there is anoxemia of the myocardium.

One is often confronted by a clinical case, the features of which are suggestive of angina pectoris in certain respects, and atypical in others. Are they cases of genuine angina? The question is, of course, of the utmost importance, but it is, nevertheless, no real concern of the issue at hand. It is one that has to do with diagnosis, and not with the pathogenesis of angina. Unfortunately there is not, at present, an absolute criterion of diagnosis of angina pectoris. So far as we know, the decision in an individual case must be determined by the outcome. If a patient with atypical symptoms of angina dies instantaneously, the presumption is that the patient actually suffered from angina during life and that a lesion producing anoxemia will be found at necropsy. If the patient does not die instantaneously, or if he does not develop the typical clinical picture of acute coronary occlusion, there must be a certain amount of doubt about the diagnosis.

We have stated that the paroxysms of pain in angina pectoris are provoked by increasing the demands on the heart and relieved by dimin-

ishing the work of the heart, and that a case of angina is likely to terminate by sudden death. This rule applies to most cases, and it remains to discuss the exceptions. These exceptions are more apparent than real.

Cases Characterized by Spontaneous Development of Pain—Although angina is usually initiated by some factor whose influences on the demands of the heart are obvious, such as effort or emotion, there are other instances in which the angina seems to arise spontaneously, as during rest or sleep. Certain of these cases can be dismissed at once, namely, those due to acute coronary obstruction. We have already pointed out the relation of these cases to angina, and further elaboration is unnecessary. Angina is really caused by a disproportion between the demands on the heart and the oxygen supply to the heart. In these cases, the oxygen supply is suddenly reduced below the requirements of the heart of even the resting person.

There are other cases not due to acute coronary obstruction. The exact physiologic changes that precede the attacks of pain are not known. However, the observations of MacWilliam⁸⁶ are of importance in this connection. They have demonstrated that sudden elevations of blood pressure or sudden increases in heart rate may occur during sleep, particularly disturbed sleep. These sudden changes may be as marked as those that occur during moderate exercise. Moreover, the reduction of blood pressure during such attacks is frequently followed by a rapid disappearance of pain (Mackenzie,¹² case 17, Schwartz⁸⁷). In other words, the changes in the circulation causing increased work of the heart may arise without effort, and they explain, in part at least, why angina occasionally arises during rest.

There is another group of cases that seems to be closely associated with attacks of paroxysmal dyspnea. That is to say, certain patients who suffer from paroxysmal dyspnea frequently have nocturnal attacks of angina. Indeed, angina may occur only at night in these patients. Without going into a discussion of the still disputed subject of paroxysmal dyspnea, it may be said that it has been shown that the attacks are preceded by a gradual increase in heart rate, blood pressure and circulatory minute volume (Eppinger, von Papp and Schwarz⁸⁸). It is conceivable that many of the attacks of nocturnal angina, occurring

⁸⁶ MacWilliam, J. A. Some Applications of Physiology to Medicine. III. Blood Pressure and Heart Action in Sleep and Dreams, Their Relations to Hemorrhage, Angina and Sudden Death, *Brit. M. J.* **2**: 1196 (Dec. 22) 1923.

⁸⁷ Schwartz, S. P. Paroxysmal Cardiac Pain, *Am. Heart J.* **2**: 497 (June) 1927.

⁸⁸ Eppinger, H., von Papp, L., and Schwarz, H. Ueber das Asthma Cardiale, Versuch zu einer peripheren Kreislaufpathologie, ed. 1, Berlin, Julius Springer, 1924.

in people subject to paroxysmal dyspnea, are brought on by these circulatory changes that precede and accompany paroxysmal dyspnea. Angina occurs, however, only in those who are already predisposed by other lesions that reduce the oxygen supply to the heart, such as coronary disease or aortic insufficiency.

Cases Characterized by Attacks not Rapidly Relieved by Rest—Little need be said about the long duration of the anginal attacks in coronary occlusion: the anoxemia is permanent and constant, and hence unaffected by rest. It is also a matter of experience that nocturnal attacks, even when they are not caused by coronary occlusion, are often of rather long duration. We think it likely that most of the cases occur in persons subject to paroxysmal dyspnea, and that the long duration of the anginal attacks may be due to the continued increase in circulatory minute volume that occurs before and during the attacks of paroxysmal dyspnea, whatever may be the fundamental cause of the increased circulatory minute volume. This relationship between certain attacks of angina and paroxysmal dyspnea has been recently pointed out by Braun.⁸⁹

Cases not Ending by Sudden Death—In some cases, the outcome is not by sudden death. Exclusive of those patients who die of some intercurrent infection or other unrelated malady, practically all others die because of failure of the heart muscle. Some develop coronary occlusion and the condition is terminated by rapidly progressive myocardial insufficiency. In others, the myocardial damage is less abrupt, and death ultimately occurs with the common picture of chronic progressive failure of the heart muscle. These latter cases furnish the examples for the statement that angina tends to disappear when heart failure supervenes. The explanation, as Mackenzie has stated, is undoubtedly due to the fact that when myocardial failure develops in these patients, their activities are so restricted on account of dyspnea and other disabilities that they are unable to exert themselves sufficiently to bring on pain.

Reference to charts 1, 2, 3 and 4 may illustrate our meaning more clearly. The figures are simple diagrammatic representations of what takes place in a patient suffering from dyspnea or angina, or both. Chart 1 shows the gradual steady increase in dyspnea, proportionate with the increase in effort.⁹⁰ After a certain amount of effort the stage

89 Braun, F. Ueber die Kombination von Asthma cardiale mit Angina Pectoris, Wien klin Wchnschr 40 1278 (Oct 13) 1927.

90 By effort, is really meant a certain effort in a given unit of time. That is to say, a certain task in a certain time may bring on dyspnea, a similar task in twice the time may cause no dyspnea. The same principle holds true for the causation of pain. By incapacity is meant inability on the part of the patient to continue his effort. The diagrams are not intended, of course, to be absolutely accurate. They are sufficiently accurate, however, to illustrate the points at issue.

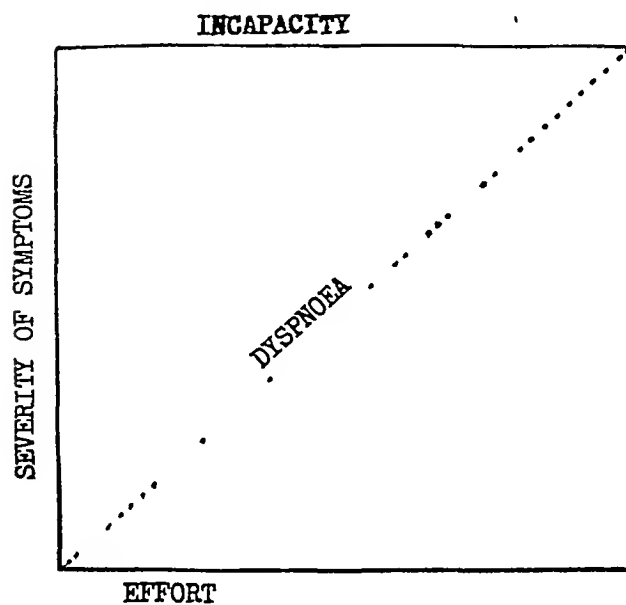


Fig 1—Illustrating the gradual increase in dyspnea, which is proportionate to the effort expended

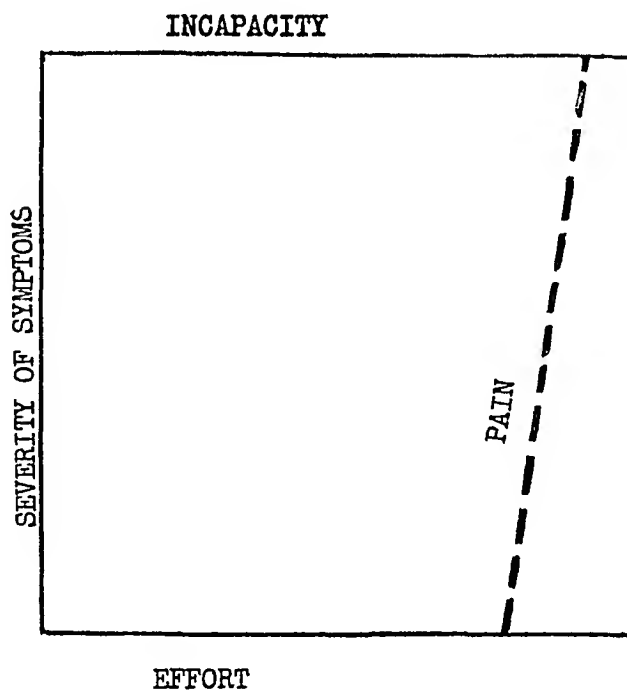


Fig 2—Illustrating the freedom from pain up to a certain point and then the sudden appearance of the symptom which increases to incapacitating intensity in a short time

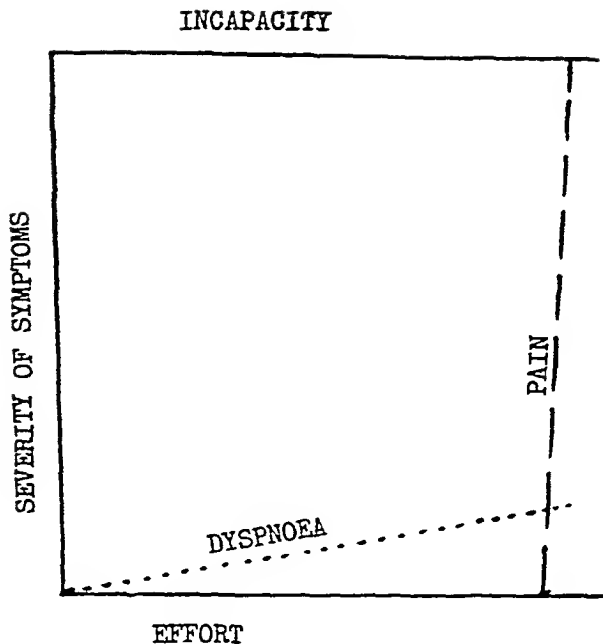


Fig 3—Illustrating the course of events in a patient suffering chiefly from angina pectoris, but also from a mild degree of myocardial insufficiency. The dyspnea increases gradually, but before this symptom has become severe enough to limit the effort of the patient, pain suddenly appears and reaches an incapacitating intensity.

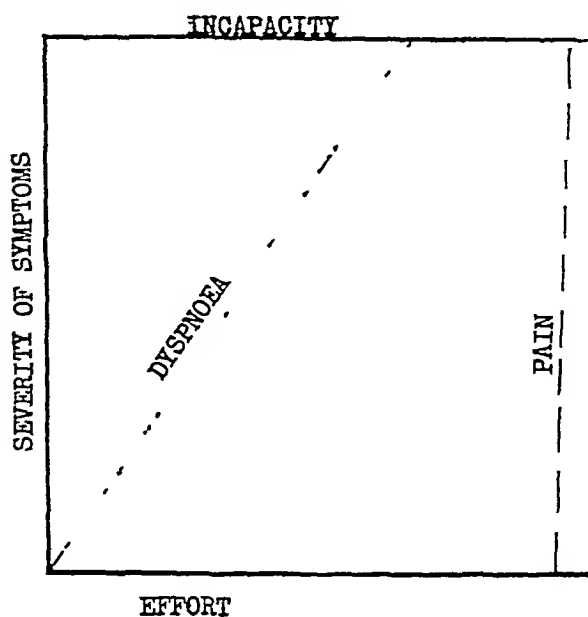


Fig 4—Illustrating the course of events in a person suffering from angina pectoris and severe myocardial insufficiency. In this case, breathlessness increases so rapidly that the stage of incapacity is reached before pain has had a chance to develop. The patient loses his symptoms of angina until myocardial function is sufficiently recovered and the effort to produce incapacitating pain again becomes less than the effort to produce incapacitating dyspnea. Pain is represented by a light dash instead of a heavy dash to indicate that it actually does not occur under the foregoing circumstances. Pain is indicated merely to draw its relation to dyspnea.

of incapacity is gradually reached, and the patient comes to a halt. Chart 2 shows the development of pain in a patient suffering from angina. It is meant to demonstrate that up to a certain point, effort does not cause any symptom of warning. Suddenly pain appears, and typically this pain reaches an incapacitating intensity with striking rapidity. Chart 3 demonstrates the development of pain and dyspnea in the same patient, the pain being the outstanding symptom. It shows that dyspnea does not become a prominent symptom in such a person, since incapacitative pain appears before dyspnea of any marked severity has had a chance to develop. Chart 4 illustrates the disappearance of pain in a person suffering from marked dyspnea (myocardial insufficiency). The dyspnea increases as it usually does, gradually and proportionately with the effort. But in this case, it increases so rapidly that incapacitation through dyspnea takes place before pain has had a chance to develop.

Finally, there are cases characterized by long remissions, in some of which cures are practically obtained. Gallavardin¹⁰ recorded thirty-eight cases in which there were remissions ranging from a year and a half to eighteen years. It seems probable that the freedom from pain is due to the development of anastomotic channels, with temporary and possibly permanent relief of the anoxemia of the affected heart muscle.

It may be seen, therefore, that the exceptions to the rule that angina is provoked by effort, rapidly relieved by rest, and likely to end in sudden death, are more apparent than real. Certainly in most cases, an adequate explanation for the exception can be found.

SUMMARY AND CONCLUSION

A critical analysis of the theories that attribute angina pectoris to coronary spasm, to disease of the aorta or to myocardial exhaustion demonstrates that these views are open to such serious criticism that they become unacceptable, on the other hand, it can be shown that anoxemia of the heart, in the sense in which we have employed the term, explains every characteristic of angina, including the likelihood of sudden death, which must be considered an integral feature of the condition. The percentage of instances in which conditions capable of producing anoxemia of the myocardium have been found in cases of undoubted angina is so high that the accuracy of the diagnosis in the few remaining instances seems open to question. We feel that an eclectic theory which admits a varied basis for angina should be abandoned. The angina pectoris of Heberden has but one cause—anoxemia of the myocardium.

FEVER IN GASTRIC AND IN DUODENAL ULCER *

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It often happens that the clinical symptoms of a disease are not in accordance with the organic lesion actually present. This fact is conspicuous in stomach diseases. To see achylia develop without any subjective symptoms is an everyday experience. The symptoms of gastritis do not develop simultaneously with the pathologic-anatomic changes in the mucous membrane of the stomach. Even such a lesion as cancer of the stomach is frequently free from any definite symptoms for a long time. This variation of symptoms is particularly characteristic of the gastric and duodenal ulcers. In some cases one finds violent pains and fatal hemorrhages, in others there is a complete absence of symptoms, mostly periodic, but sometimes throughout the course of the disease. This behavior can be so constant that periodic latency is diagnostic in certain forms of ulcer. In such a case, however, the pathologic-anatomic picture is in keeping with the symptoms, as it is mostly characterized by negative observations. The classic description of ulcer of the stomach suggests the picture of a simple defect of the mucous membrane with no reaction about it, and this fact is indicated by the term "ulcus simplex."

In the last six or seven years, however, this classic "simplicity" in the anatomic relations of ulcer of the stomach has encountered increasing criticism, which I shall discuss later. As to the clinical symptomatology, on the other hand, there has not been great progress in the last generation, in spite of the marked development of methods of examination. Methods are lacking for the determination of when the ulceration takes place, when it is healed and what really does happen in the latent periods. I have attempted to attack this problem from various angles, but here I shall discuss only an analysis of the temperature in gastric and duodenal ulcers.

The fact that fever occasionally is present in ulcer is not altogether unknown. But it has not received the attention it deserves with regard to its diagnostic and practical significance. I have not found this subject mentioned in any of the many textbooks I have examined. From this fact I conclude that the occurrence of fever in gastric ulcer is not generally known. The special literature on ulcer of the stomach mentions now and then that fever can be associated with hemorrhages, but so far

* Lecture delivered at the Northern Medical Congress in Copenhagen, July, 1927

I have succeeded in finding only one paper which mentions fever as a complication of nonbleeding ulcers. This was an article by Kioner,¹ which appeared recently. He cited one earlier author, Lorenz, who was said to have found fever in 23.5 per cent of his 179 patients with ulcer of the stomach. Kioner studied 300 patients with ulcers from Strauss' department in Berlin, and found fever, without any demonstrable cause, in 17.5 per cent of them. It should be mentioned, however, that Kioner regarded a single rise of temperature to 37.5 or 37.6 C as fever.

My material comprises 386 cases from the Municipal Hospital (Copenhagen), department III, during the years 1922-1926. This number includes all the cases I diagnosed as ulcer. I investigated the frequency of fever in these cases, and I did not consider an isolated rise of temperature as "fever," no matter how high the temperature rose. I have included only those patients in whom the fever lasted several days. I found these fever periods in 207 of the 386 patients, that is, in 53.5 per cent. Naturally one must exclude all cases in which there was the slightest indication that the fever might have been due to causes other than the lesion in the stomach. For that reason, I analyzed each individual case report, and found that twenty-eight cases had to be left out (among these were active and suspected cases of pulmonary tuberculosis, pyelitis and cholelithiasis. In addition there were seven patients in whom the temperature rose shortly before the onset of menses, so that a premenstrual rise of temperature had to be taken into consideration).

After these cases are deducted, my material includes 358 patients, of whom 179 had fever, that is, 50 per cent. The fact that I found fever in 50 per cent of the patients while Kioner found fever in 17 per cent might well be due to differences in the kinds of lesions. It is reasonable to assume that the fever is less frequent in old and latent lesions than in acute conditions. That there really is such a difference between the two groups is evident on a comparison of the frequency of manifest hemorrhage (hematemesis and melena, but not the occult bleeding). In Kioner's group the hemorrhages occurred in 25 of 300 patients, or 8 per cent, I found hemorrhages in 161 of 386 patients, or 41.7 per cent. As the fever most often is associated with hemorrhage, one will readily understand the difference between the groups. This difference is due to the fact that the Municipal Hospital admits only patients with acute cases. This might also explain why the specialists in diseases of the stomach have not attached so much importance to the fever, as the patients who consult them usually are those in whom the condition is chronic.

¹ Kioner. Ueber Fieber bei Ulcus ventriculi et duodeni, Deutsche med Wchnschr 52 1777, 1926.

Leube mentioned the complication of fever in gastric ulcer, but he considered the fever an exception. Eichhorst (1887) claimed occasionally to have seen a mild fever when the intestines contained a large amount of blood after hematemesis but as the temperature returned to normal on elimination of the blood, he regarded the rise of temperature as an absorption fever. Strumpel stated that a slight rise of temperature, the so-called anemic fever, was common subsequent to hematemesis. However, Otto Leichtenstern² (1891) was the first one to investigate this relation systematically, and he used the term "*febris methematemetica*," which he defined as "a fever that sometimes is quite mild, sometimes rather high, sometimes perfectly atypical, irregular and

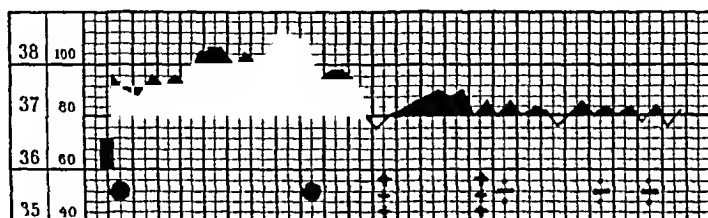


Chart 1—Gastric ulcer in a man, aged 60. In this and the following curves, all the rises of temperature above 37 C are filled in black. A black square indicates hematemesis. A black sphere indicates melena. + indicates weak, ++ medium and +++ strong benzidin reaction, — indicates negative benzidin reaction.

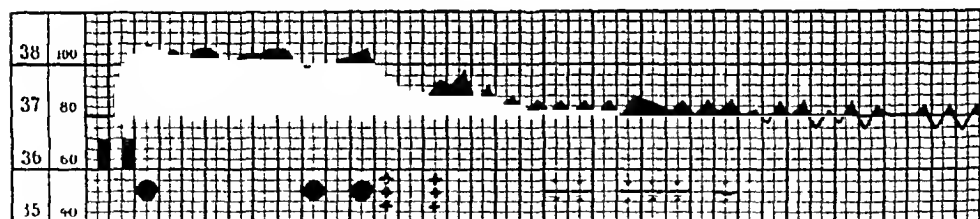


Chart 2—Gastric ulcer in a man, aged 51.

remittent, sometimes continuous for several days." He found this fever to be a frequent, even a regular, phenomenon in hemorrhages from gastric ulcer, and he regarded it as an absorption fever because it usually did not appear until two or three days after the hematemesis while the patient still was constipated. Most other clinicians who have dealt with this question at all (for instance, Riedel, Stahelin, Ewald,³ Fleiner) subscribe fully to Leichtenstern's view. I have not found any

² Leichtenstern. Intravenöse Kochsalzinfusion bei Verblutungen, *Samml. klin. Vortr.* 25:260, 1891.

³ Ewald. Magenkrh., *Eulenburg's Realencyklopädie der gesamten Heilkunde*, Vienna and Leipzig, Urban & Schwarzenberg, 1897, vol. 14, p. 287.

tables that illustrate this question except in a report by Jacobs⁴ and in the recent work by Kroner, who found fever in eleven of twenty-five patients with manifest hemorrhages, i.e., in 45 per cent. This figure is considerably lower than that of my group, probably owing to the more acute character of my cases.

In my 358 cases I have taken into account only those hemorrhages which were definitely demonstrated in the hospital. Hemorrhages which occurred while the patients were at home without subsequent occult bleeding in the hospital are not included. There are 138 cases of definite hemorrhage, and fever was associated with the hemorrhage in 125 cases, or 90.5 per cent. In some of these cases, however, a possible source of error must be taken into consideration. Thirty-five of the patients were

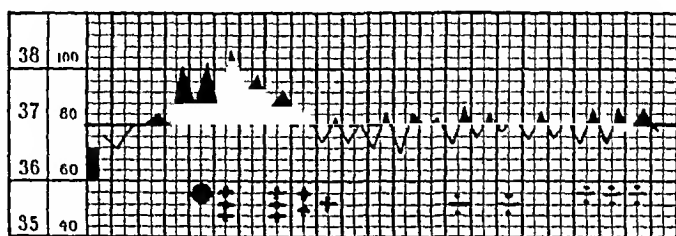


Chart 3—Gastric ulcer in a man, aged 41

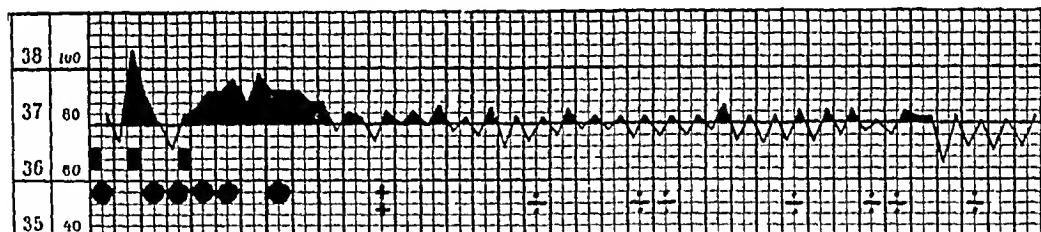


Chart 4—Gastric ulcer in a man, aged 32

treated with an injection of gelatin, this procedure can cause a rise of temperature for from one to two days. Thirty-two of the patients, however, had fever previous to the injection of gelatin. Hence, there were only three cases in which the effect of the gelatin cannot be disregarded with absolute certainty. If these three cases are excluded, of a total of 138 patients there remain 121, or 87.5 per cent, in whom fever was present.

CAUSES OF FEVER

What can be the cause of this fever? It can be taken for granted that the anemia in itself did not cause the fever. That this is true is evident from my material, as many patients with a mild anemia had high fever, and numerous patients with a most severe anemia showed a

⁴ Jacobs, cited by Kroner (footnote 1)

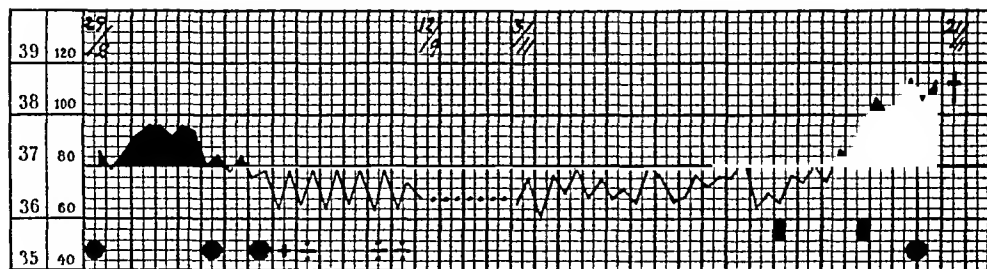


Chart 5—Man, aged 42 The first rise of temperature occurred in connection with melena Nearly three months later, hematemesis occurred two times, followed by rise of temperature and death with symptoms of anemia Autopsy peptic ulcer of jejunum with erosion of vessel No other demonstrable cause of elevation of temperature, in vivo or at autopsy

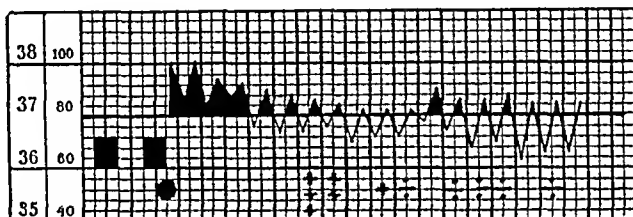


Chart 6—Juxtapyloric ulcer in a man, aged 45



Chart 7—Juxtapyloric ulcer in a man, aged 53

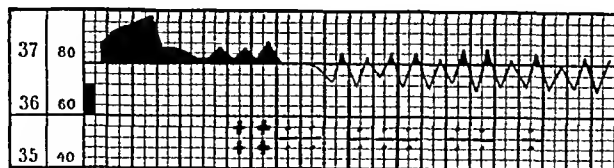


Chart 8—Gastric ulcer in a man, aged 48

marked rise of temperature only for a few days after the hemorrhage, while the anemia persisted or even increased without any fever. A comparison of the patients with and without fever might give some information on this subject. The blood was examined immediately after the hemorrhage in nine patients who did not have subsequent fever. The hemoglobin percentage was 55 or more in all of them. In the febrile cases, the hemoglobin content was above 55 per cent in seventy-two patients and below 55 per cent in thirty-four patients. Kroner's result is analogous to mine. But when Kroner concludes from this result that the fever is dependent on the "violence" of the hemorrhage, I cannot agree with him. For, if the hemorrhage and the fever

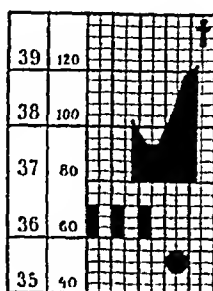


Chart 9—Hematemesis and death with symptoms of anemia in a woman, aged 44. Autopsy showed ulcer of small curvature with erosion of artery. Other observations at autopsy were negative.

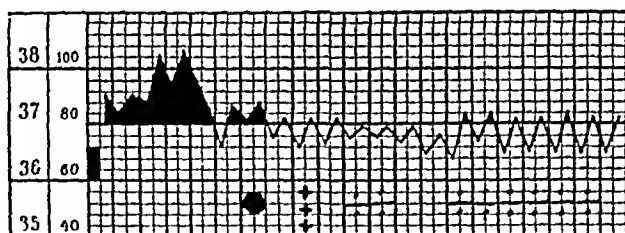


Chart 10—Juxtapyloric ulcer in a man, aged 39.

are caused by the same process (inflammatory, for instance), then this process might conceivably have accomplished the "violence" of the hemorrhage and the fever alike, without these being directly dependent on each other. Two of my afebrile cases are of interest in this connection, both patients having had profuse hemorrhages which caused death in a few days. In neither did the temperature exceed 37.2 C. Autopsy revealed in both instances that an erosion of the vessel wall was the cause of the profuse hemorrhage. One can readily understand that when these ulcers did not cause a rise of temperature previous to the hemorrhage, fever would not necessarily result from the minimal erosive process that is required for the perforation of a vessel already laid bare. On the other hand, in an acute and febrile inflammatory process, which

rapidly destroys the mucous membrane and in doing so perforates a vessel, "violent" hemorrhage and fever can appear simultaneously without being caused by each other. In the last ten years in the department, autopsy material was obtained from five patients who had died from hemorrhage in ulcer of the stomach without the temperature rising shortly before death. In all these cases the ulcers were old and callous

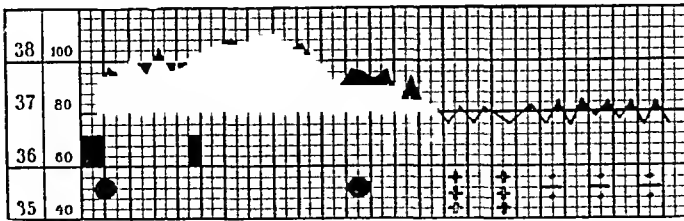


Chart 11—Duodenal ulcer in a man, aged 63

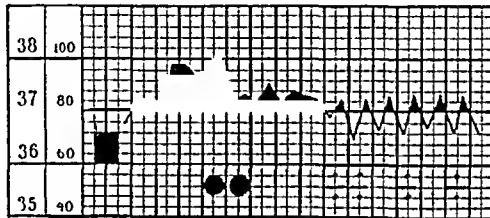


Chart 12—Gastric ulcer in a woman, aged 64

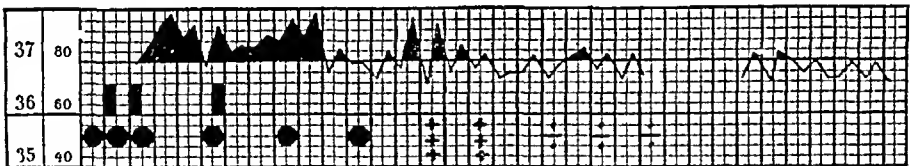


Chart 13—Gastric ulcer in a man, aged 32

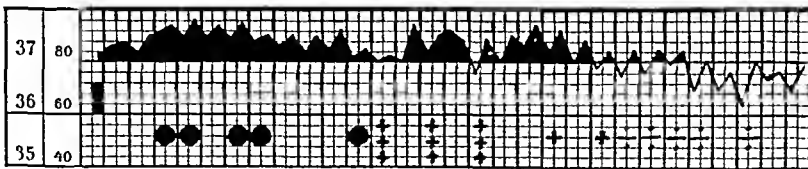


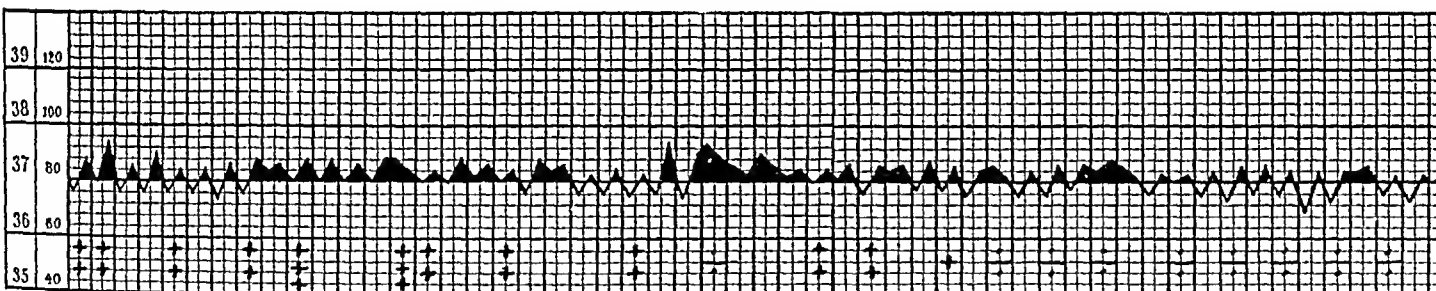
Chart 14—Gastric ulcer in a woman, aged 52

In three death occurred from the erosion of a dissected artery at the bottom of the ulcer. In addition, I have one case in which an operation revealed a callous ulcer with some scar formation. Large hemorrhages had occurred repeatedly, without any fever, about three weeks previous to the operation. If this point of view is correct, one would expect the afebrile hemorrhage to be most frequent in old ulcers, and I found that

twelve of the thirteen patients with afebrile hemorrhages had ulcer symptoms for several years (from two to thirteen years) In only one case were the symptoms of a recent date (two months) On the other hand, all the apparently recent ulcers were found in the febrile group, namely, nineteen patients, in whom the first symptoms had appeared within the week before examination (the hematemesis was practically the first symptom in the stomach in these cases) Collecting all the febrile cases with first symptoms of not more than two months' duration on admission, I find ninety-two patients in this group, that is, 74 per cent Thus all the recent ulcers occur in patients of the febrile group, while old ulcers are found both in the febrile and the afebrile groups Fever is fe-



A



B

Chart 15—Gastric ulcer in a woman, aged 55 The hemorrhage lasted eighty-nine days, the rise of temperature, ninety-six days

quently associated with an acute exacerbation of the old process But, of course, old ulcers can also give rise to fever when they become secondarily infected My experience demonstrates, I believe, that acute ulcers and acute exacerbations of old ulcers frequently are connected with fever, apart from the fever of secondary infection

I have tried to answer the question whether absorption or decomposition of large amounts of blood in the intestines can give rise to fever For that reason I have compared the ulcer with other conditions in which a great deal of blood is poured into the intestines The hemorrhages from esophageal varices seem most appropriate for such a comparison During the last ten years I have performed seventeen autopsies

in which esophageal hemorrhage was the cause of death. Three of the patients had complications which gave sufficient cause for the fever present, and in one patient the temperature was taken once only (37.9°C) shortly before death. The temperature was normal in the remaining thirteen patients for from one to four days after the start of the hemorrhage. Most of these patients, however, died in from one to three days after admission, and the others soon developed febrile complications (bronchopneumonia, otitis, phlegmons). In only two patients did the temperature remain normal for four days after the onset of the hemorrhage. This did not happen once after a severe hemorrhage in my patients with ulcer of the stomach. Autopsy was not performed on seven patients who died of hemorrhage from esophageal

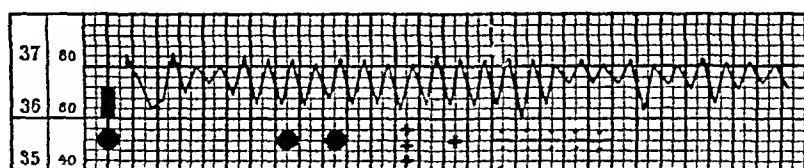


Chart 16—Hemorrhage from esophageal varices in a man, aged 48

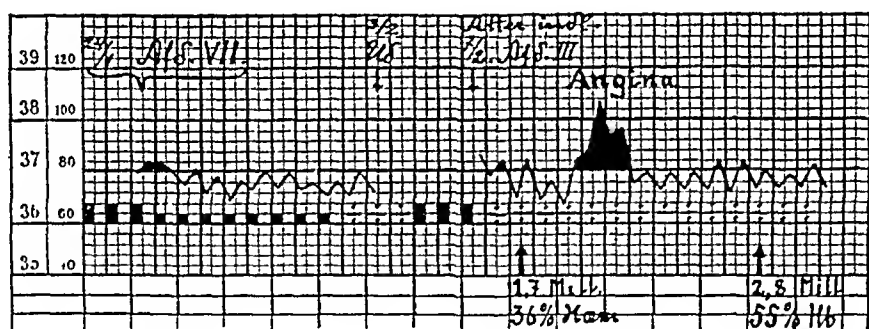


Chart 17—Epistaxis in a man, aged 48. In this chart the black squares indicate bleedings from the nose. At the cessation of bleedings he had 1,700,000 red corpuscles. That the anemia was due to the bleeding is evident, as he had 2,800,000 red corpuscles ten days later.

varices. Four of these had complications which explained the mild fever, the other three had a normal temperature throughout. In one of these patients (fig 16) the number of red blood cells decreased to 2,500,000. In the patients with ulcer such a case did not occur without fever. Of course, the diagnosis of hemorrhage from esophageal varices is never absolutely sure without an autopsy, but such a case proves that large amounts of blood can pass through the intestines without causing fever.

The hemorrhages from cancer of the stomach generally are not suitable for comparison, because the amount of blood usually is small, and because fever often develops without hemorrhage. However, I

encountered twelve patients with cancer of the stomach with severe hematemesis. Five of these had a normal temperature for at least six days after the hemorrhage. One would think that epistaxis would be suitable for comparison, but most of my cases cannot be used for this purpose because the case reports do not indicate how much blood passed through the intestines. Only two of my cases allow any conclusion in that respect. In the first case, for two weeks the hemorrhage was sometimes profuse, sometimes continuously oozing, the count of red corpuscles decreased to 1,700,000. Nevertheless, the temperature remained normal (apart from a complicating angina [fig 17]). In the second case, the temperature remained normal for five days after an epistaxis, which was followed by several tar-colored stools.

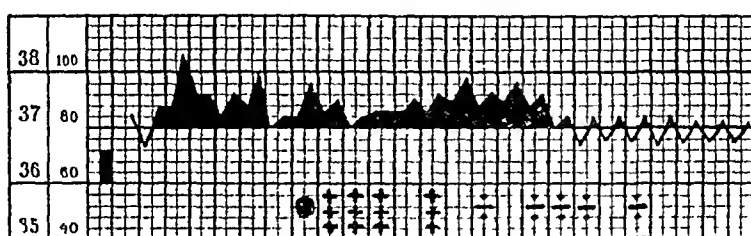


Chart 18—Gastric ulcer in a woman, aged 74

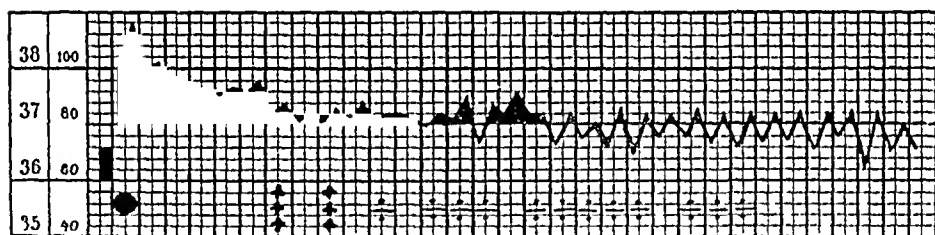


Chart 19—Gastric ulcer in a man, aged 38

Finally, I saw seventeen patients with hemorrhage from gastric ulcer without rise of temperature. This proves that not every accumulation of blood in the intestines causes fever.

The entire control material needs to be increased and additional investigations must be carried out before one can definitely decide the question whether accumulation of blood in the intestinal tract can of itself give rise to fever, but even from the material at hand, one can conclude that not every accumulation of blood in the intestinal tract is followed by fever. And, fortunately, my experience with ulcers gives some information on this question.

If the blood in the intestines were the only cause of the fever, one would expect a certain relation between the rise of temperature and the retention of the blood in the intestinal tract. And such a relation must be present in one respect, namely, with regard to the height of the fever. The highest temperature was usually present while the patient was kept

constipated, as Eichhorst has already observed. In my patients the fever frequently subsided at the same time that the first bowel movement occurred, but this was not conclusive, as I tried to keep the patients constipated until they felt perfectly well, i.e., until the fever ceased. I found it likely that decomposition of the blood in the intestines caused fever or at least increased a preexisting fever, but the fever was not at all proportionate to the amount of blood in the intestines. The elevated tem-

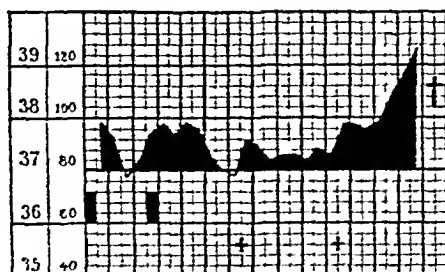


Chart 20—Woman, aged 68. Autopsy. Ulcer of small curvature. No other demonstrable cause of fever.

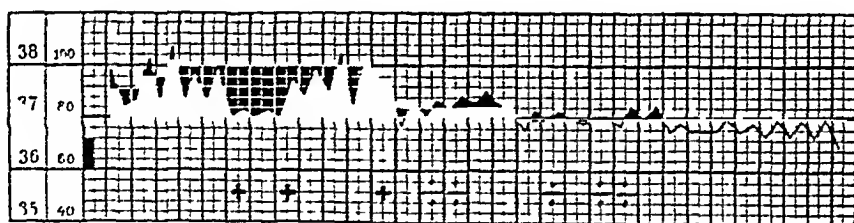


Chart 21—Gastric ulcer in a woman, aged 20.

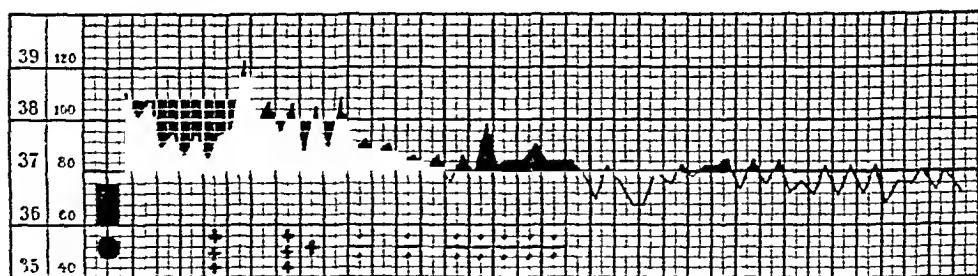


Chart 22—Juxtapyloric ulcer in a man, aged 39.

perature persisted in a number of cases a long time after the last trace of blood had disappeared from feces, and the test was done with the sensitive benzidine reaction (figs 18 to 32). This relation was found in 68 of 138 cases and was indicated in many more cases.

However, one can proceed a step farther. One can examine those cases in which neither hematemesis nor melena were present, and in which the occult bleeding could be demonstrated only with benzidine

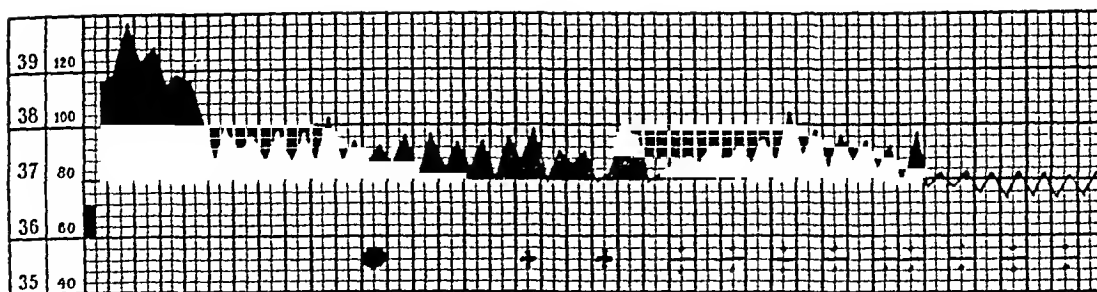


Chart 23—Gastric ulcer in a woman, aged 39

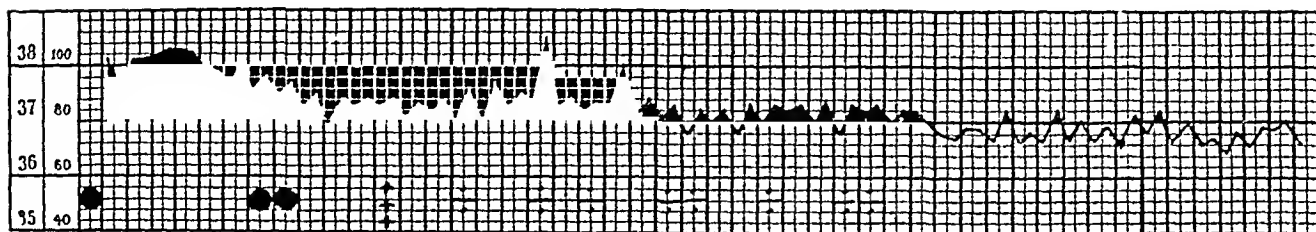


Chart 24—Juxtapyloric ulcer in a woman, aged 33

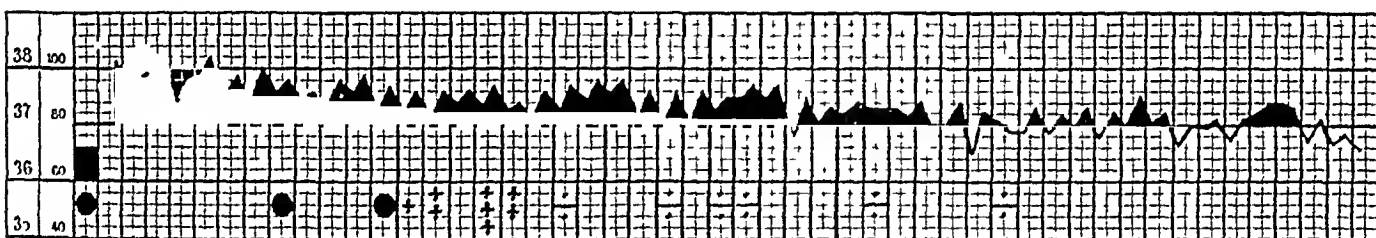


Chart 25—Gastric ulcer in a woman, aged 47

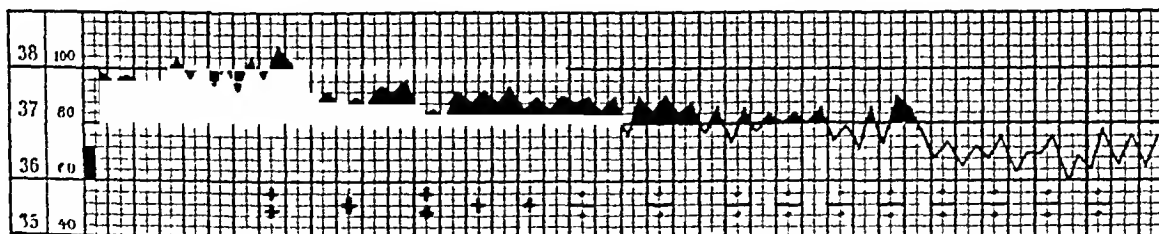


Chart 26—Juxtapyloric ulcer in a woman, aged 67

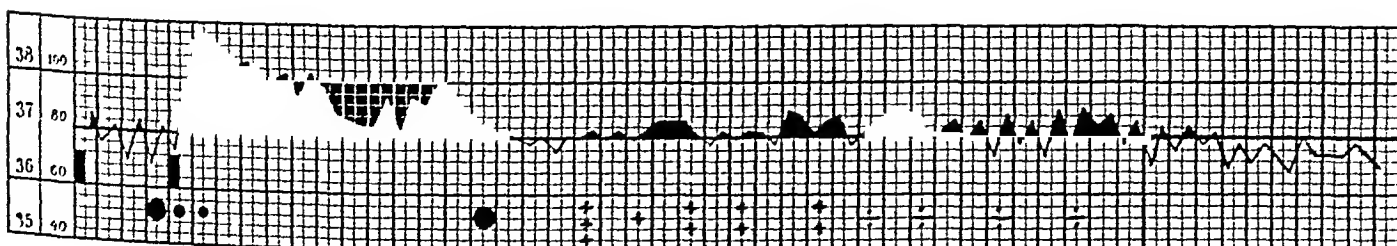


Chart 27—Duodenal ulcer in a man, aged 67

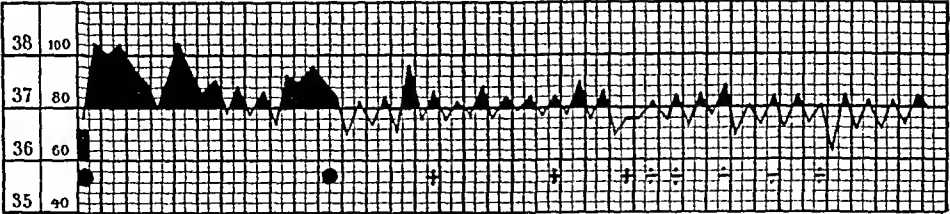


Chart 28—Duodenal ulcer in a man, aged 30

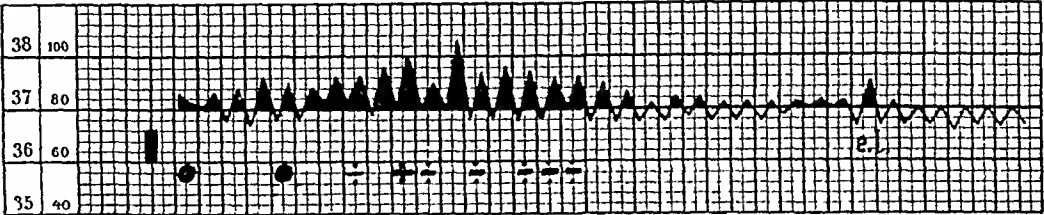


Chart 29—Gastric ulcer in a man, aged 41

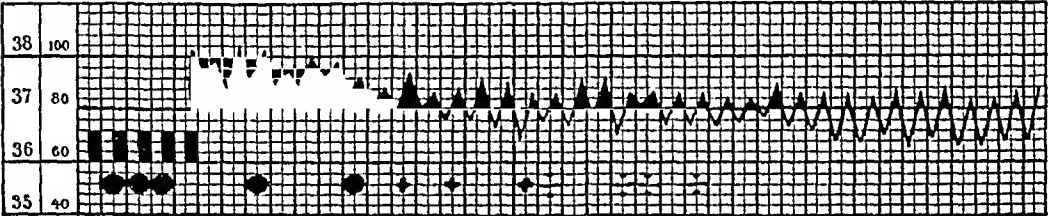
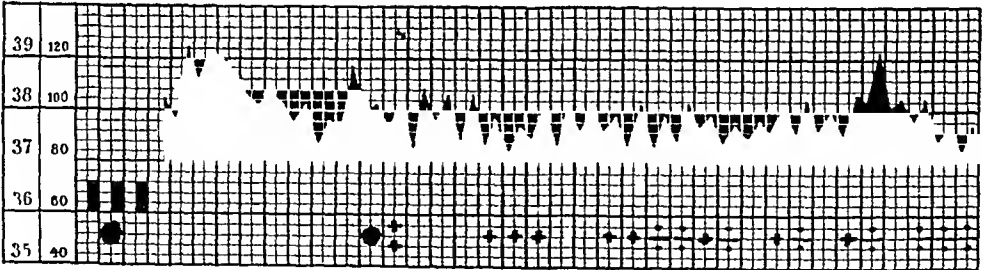
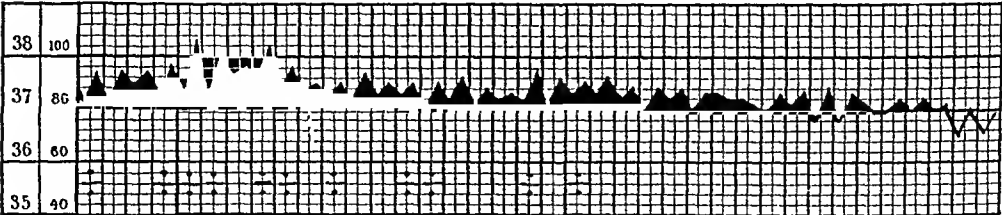


Chart 30—Juxtapyloric ulcer in a man, aged 55



A



B

Chart 31—Juxtapyloric ulcer in a woman, aged 64

(figs 33 to 37) According to Gregersen, the weakest benzidine reaction indicates a total of 1 Gm of blood in the entire intestinal tract, and it is not possible that such small amounts of blood can cause fever from absorption or decomposition. I have seen twenty-eight such cases of occult bleeding, and twenty-one of these, or 75 per cent, were febrile. The bleeding could not be considered established in three of the twenty-eight patients, as the benzidine reaction was positive only once, i.e., immediately after admission, thus the reaction can have been due to the

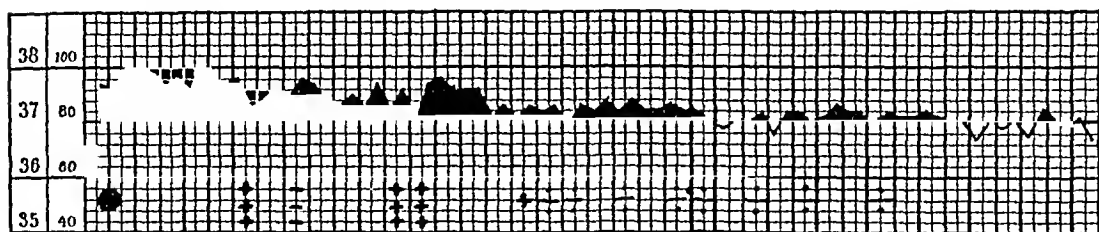


Chart 32—Juxtapyloric ulcer in a man, aged 45



Chart 33—Ulcer of small curvature in a woman, aged 75

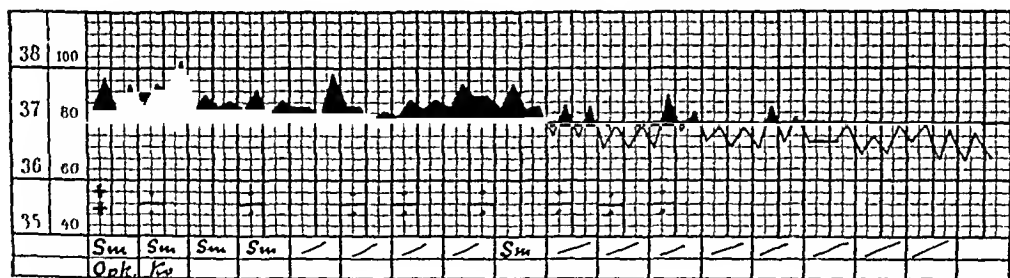


Chart 34—Juxtapyloric ulcer in a man, aged 51

consumption of meat before admission. If these three patients are left out, the fever percentage rises to 84 per cent, and this is about the same fever percentage as that in manifest hemorrhages.

In order to prove that the fever is due to some cause other than the hemorrhage, one should demonstrate the presence of fever in patients with ulcer but no hemorrhage (figs 38 to 44). In the 386 patients with ulcer, there were 13 of this type. When one considers that 40 per cent of the 386 patients were admitted to the hospital because they had

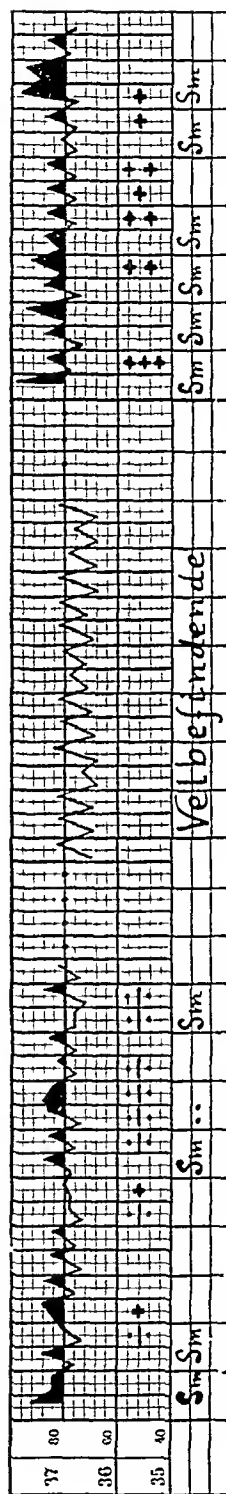


Chart 35—Ulcer of small curvature in a man, aged 49 Sm means pain, Velbefindende, no symptoms That the temperature elevation was not due to the pains is evident, as the pains did not set in before night, while the temperature rose in the evening

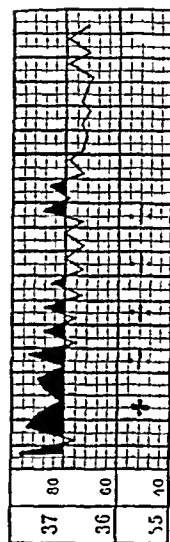


Chart 36—Juntapyloric ulcer in a man, aged 45

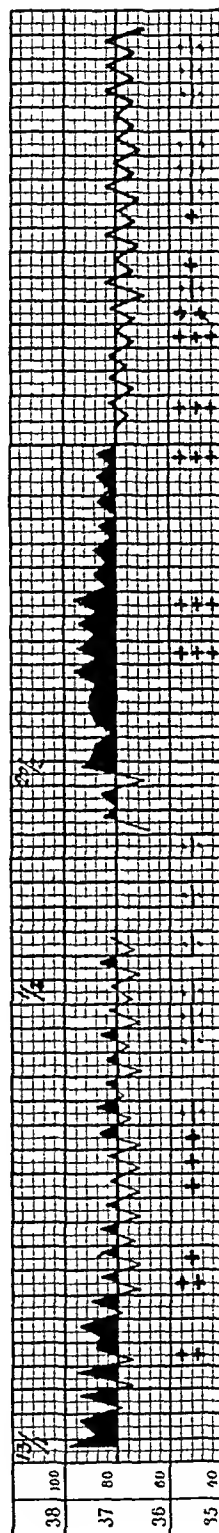


Chart 37—Duodenal ulcer in a man, aged 37

manifest hemorrhage, thirteen is not such a small number. They comprise 65 per cent of the patients with nonbleeding ulcers. It is a foregone conclusion that the large majority of chronic latent ulcers are afebrile. Autopsy was done on two of the thirteen patients with febrile nonbleeding ulcers. Both ulcers were old, large and callous, with a foul base. In such cases it is reasonable to assume that the ulcer was the site of a secondary infection. The other eleven ulcers were juxtapyloric or duodenal. In the group "ulcer with manifest hemorrhage," the diagnosis of juxtapyloric and duodenal ulcer was equally frequent in the febrile and the afebrile groups (50 and 47 per cent, respectively).

From this investigation I think I am justified in the conclusion that many patients with gastric and duodenal ulcer develop a rise of

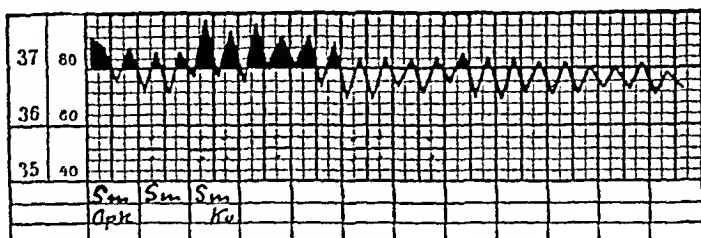


Chart 38—Duodenal ulcer in a youth, aged 19

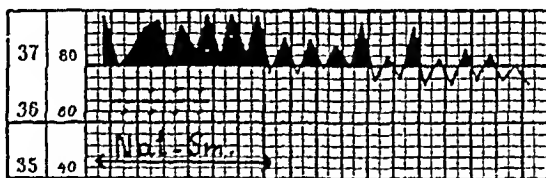


Chart 39—Duodenal ulcer in a man, aged 29. The rise of temperature was not due to pains, as they occurred at night several hours after the rise of temperature

temperature which is not associated with hemorrhages. Large amounts of blood in the intestines, apparently, are capable of increasing this fever, and, perhaps, the decomposition of the blood can give rise to fever, but this question requires further investigation. This fever may vary to some extent, but it most decidedly tends to be continuous and with relatively small variations.

I think it will prove of some practical value to take these temperatures into account. In some of my patients, a slight elevation of the temperature was the only demonstrable sign of an otherwise latent period. Even though all other symptoms were absent, the temperature still indicated that the ulcer itself or its fundamental cause had not yet been cured. Since I have realized this fact, I have ordered the patients diet and rest in bed accordingly. A slight elevation of the temperature can sometimes persist for weeks, and I believe it to be of some conse-

studied the fresh material from resections, and said that he was "astonished" the first time he looked at a recently removed and carefully prepared ulcer. Even as late as in 1919, Ashoft wrote that "any special deposits on the ulcer, exudates and necrotic masses, are practically absent," and that "the lack of inflammatory changes in the surrounding mucous membrane usually is conspicuous." The first contradictory statement, as far as I have been able to find out, came from Faber's department when G. Lange⁷ (1910) mentioned some more or less marked inflammatory processes in about half of his material obtained

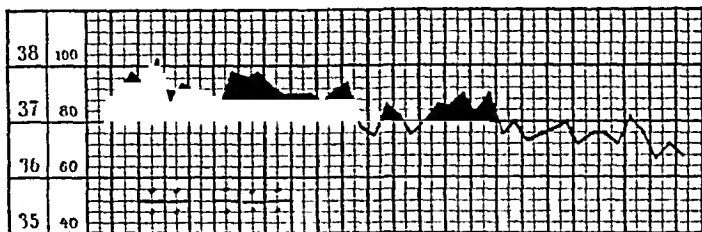


Chart 43—Gastric ulcer in a woman, aged 24

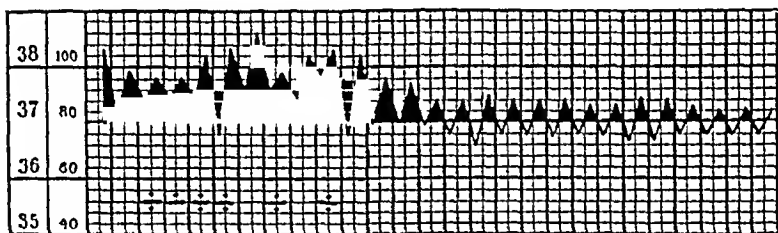


Chart 44—Juxtapyloric ulcer in a man, aged 32

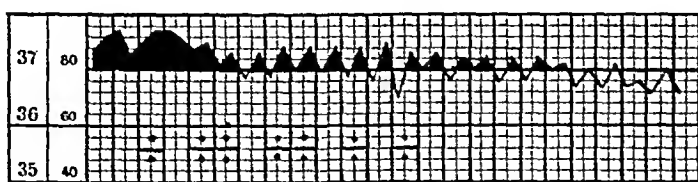


Chart 45—Juxtapyloric ulcer in a woman, aged 27

by resections. These, however, were mostly some very old ulcers. In 1921, Faber wrote, in his treatise on acute and chronic gastritis in Kraus and Brugsch's textbook, that the acute hematogenous gastritis which develops subsequent to infections does not show any macroscopic signs of gastritis, but that the microscopic examination reveals a marked round cell infiltration between the glands, usually associated with a marked development of lymphoid tissue. This process continues farther in a number of cases, forming small hemorrhagic erosions which can develop

⁷ Lange, G. Studier over den kroniske Gastritis, Inaug. Diss., Copenhagen, 1910.

into small ulcerations and result in an acute ulcerative gastritis. These erosions can give rise to hematemesis with more or less extensive inflammation of the mucous membrane, particularly around the ulcerations. "When the gastritis has persisted for some time, one can find that some of the small ulcerations extend farther out and particularly downward, forming a transition to true simple ulcers."

In 1921, Askanazy published a report on forty-four resected ulcers in which he "almost constantly" found even macroscopically four different layers: (1) a layer of exudate, (2) beneath this a 1.3 by 1.5 mm thick opaque stratum, the "fibrinoid or diphtheroid necrotic zone", (3) a layer of granulation tissue, often several millimeters in thickness, and (4) deepest, a layer of scar formation—at least in the older ulcers. The three first layers were of such a delicate structure that even the weakest stream of water at autopsy would remove them, not mentioning the postmortem digestion. It is not any wonder that the dissecting anatomist does not find these layers. In the fibrinoid zone Askanazy always found numerous leukocytes and often circumscribed "abscess-artige Erweichungsherde". He considered the fibrinoid layer to be the product of an ever-developing, at least periodic, acute inflammation.

In the last two or three years Konjetzny⁸ studied this resection material, and he came to the conclusion that a chronic gastritis is present with every ulcer of the stomach or duodenum, particularly in the region of the antrum, while the fundus usually does not show this condition. In forty-one resections for duodenal ulcer, he found gastritis and duodenitis present in 100 per cent, and in 54.5 per cent of these cases there were additional inflammatory defects of the mucous membrane outside the ulcers, i.e., erosions. He was strongly supported by Kalima,⁹ who claimed that ulcers always were associated with a diffuse or focal gastritis and often with superficial ulcerations, and that this lesion was most marked in the pyloric area of the stomach and along the small curvature, while the other sections of the stomach were affected but slightly. There is no doubt that these erosions developed on bases of the gastritis and appeared in groups. The intermittent course of the gastritis was probably the cause of the periodic appearance of the symptoms of ulcer. In this connection, Kalima mentioned that Faber had emphasized the fact that the uncomplicated chronic gastritis had a tendency toward an intermittent course. This helped to explain the characteristic exacerbations of peptic ulcer.

⁸ Konjetzny: Surgical Aspects of Chronic Gastritis, *Arch f klin Chir* **129** 139, 1924, Inflammatory Basis for Duodenal Ulcer, *Deutsche Ztschr f Chir* **184** 85, 1924, Inflammatory Genesis of Ulcer of Stomach and Duodenum, *Arch f Verdauungskr* **36** 189, 1925.

⁹ Kalima: Chronic Gastritis and Gastric and Duodenal Ulcers, *Acta chir Scandinav* **58** 122, 1925.

Schmincke¹⁰ found gastritis in 100 per cent of his patients with ulcers, von Haberer,¹¹ Heidenheim, Duschl,¹² Orator¹³ and Finsteier came to similar results in reality, although their theoretical interpretation of these results were somewhat divergent. In 1926, Bohmansson¹⁴ published the results of 185 resections in the hospital of Numeaa. Almost every section showed macroscopically a pronounced redness of the entire pyloric area, which was frequently swollen and edematous, while the fundus was much paler. This condition seemed to be constant in gastric ulcer and less constant in duodenal ulcer. Microscopic examination showed a constant increase of the plasma cells and polymorphonuclear leukocytes in the form of perivascular infiltration. The pus cells not infrequently accumulated as miliary abscesses. He considered the gastritis to be the primary lesion, and thought that the term "gastritis ulcerosa" would be correct. I reviewed his material in the hope of finding some recent and acute cases. However, it contained only six cases, but even these constantly showed considerable inflammatory changes in all the tissue layers with a macroscopic swelling and redness of the mucous membrane.

I will cite his case 63, because it is the only one in which the temperature is mentioned.

The patient was admitted with a "slight" hematemesis and a temperature of 38.7 C. The fever lasted for one week. The symptoms in the stomach had been present for two months only. At the operation three ulcers were found above the angle. At least one of these was of recent date. The whole pyloric portion was considerably thickened. On macroscopic examination of the resected specimen the pyloric portion was found to be hardened, infiltrated, somewhat swollen and red, and there was a sharp line of demarcation between the normal mucous membrane of the fundic portion and the swollen mucous membrane of the pyloric portion. Microscopic examination showed a considerable plasma cell infiltration with occasional pus cells.

This case, then, was one of ulcer with a slight hemorrhage, considerable inflammation and fever—exactly the combination of symptoms that I take to be characteristic. Of course, to operate when an ulcer is in *statu nascendi*, so to speak, will always be a rare coincidence, but operations have been done at a still earlier stage of the ulcer formation,

10 Schmincke. *Anatomische Befunde an Ulcusmagen*, München med. Wchnschr., 1923, p. 1525.

11 Haberer. *Zentralbl. f. Chir.* **51**, 67, 1924.

12 Duschl. *Anatomy of Stomachs Predisposed to Ulcer*, *Deutsche Ztschr. f. Chir.* **187**, 55, 1924.

13 Orator. *Gastric Ulcer*, *Mitt. u. d. Grenzgeb. d. Med. u. Chir.* **35**, 214, 1922, *Beitr. z. Magenpath.*, *Virchows Arch. f. path. Anat.* **255**, 639, 1925.

14 Bohmansson. *Surgical Treatment of Gastric and Duodenal Ulcers*, *Acta chir. Scandinav.* **60**, 1, 1926.

namely, before the ulceration took place. One of Borgbjærg's¹⁵ (1922) two cases is of special interest. The operation did not reveal an ulcer, but a flat, purulent infiltration of the mucous membrane 2 cm wide. On microscopic examination Melchior found considerable purulent changes, especially in the mucosa, with thickening of the submucosa and considerable diffuse cell infiltration, and a large portion of the gland crypts had undergone necrosis and liquefaction. It is more than probable that such a lesion is just about to become an ulcer, and it most likely will cause some fever.

More and more cases of this kind are being reported. Thus Konjetzny (1924) reported no less than nine analogous cases in which he performed operations. Most of the patients presented typical symptoms of ulcer for years—with hematemesis in four of them—and yet the operations did not reveal ulcer but chronic gastritis. Orator reported three cases of the same nature.

Thus, one may find every "ulcer symptom," periodicity, pains at night, hematemesis and even pyloric stenosis as in Borgbjærg's case, all present in chronic gastritis—a fact which Faber also has emphasized. One then naturally asks if, after all, the gastritis in gastric ulcer is not the lesion which gives the so-called symptoms of ulcer. The symptom that has been the subject of my investigation, namely, the fever, is reasonably referable to the gastritis. At any rate, it is evident from the quoted cases that the gastritis frequently is of such an inflammatory nature that the presence of fever seems reasonable.

COMMENT

When one looks at the whole matter from this point of view, the question is not how often the bleeding ulcers are associated with fever, but how often fever is connected with those lesions of the stomach from which ulcers develop. In 121 cases of manifest hemorrhages with fever, the diagnosis of ulcer was certain in fifty-nine patients, for in these patients the diagnosis was based on autopsy, on operation or on the presence of characteristic subjective symptoms, roentgen-ray observations, positive evidence in the functional stomach test and hemorrhage. Thirty-two additional patients showed characteristic signs of a lesion in the stomach, a characteristic anamnesis and hemorrhage—making a total of ninety-one patients or 75 per cent. In twenty-two patients the hemorrhage occurred in direct connection with a period of dyspepsia, these together with those just mentioned make 113 patients, or 93.5 per cent, with symptoms in the stomach and hemorrhage. The lack of objective signs apart from the hemorrhage in the last twenty-two cases

15 Borgbjærg. Ulcerative Gastritis, *Arch f Verdaauungskr* 30 73, 1922

was due to the fact that most of the lesions were acute, so that the characteristic signs had not had sufficient time to develop, and in several instances the lesion was cured before stomach tests could be made, as such examinations were carried out only when the patient had been free from symptoms for some time after the hemorrhage. In one of the remaining patients, the autopsy revealed a chronic gastritis of the same kind as that in Borghjaerg's case. Finally, eight patients are left in which the only symptom was the hematemesis, in these cases the diagnosis was supported solely by the fact that no other cause of the hemorrhage could be found. If the doubtful cases are deducted, there were 113 cases (87 per cent) with fever in 130 cases of lesions of the stomach with manifest hemorrhage. If, however, I take into account only definite ulcers, fifty-nine of sixty-five cases, or 91 per cent, were febrile. These corrections in no way alter my first figures (87.5 per cent), because such corrections are not to be made in the groups "occult bleeding" and "no bleeding," as these groups comprise only objectively demonstrable ulcers. This shows that whether I merely take the definite ulcers into account, or I include all "stomach lesions with hemorrhage" (apart from cancer), I find fever present in nine tenths of all the patients.

BASAL METABOLISM

II THE BASAL METABOLIC RATE IN RELATION TO SYMPTOMS AND SIGNS IN HYPERTHYROIDISM *

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The purpose of this paper is to compare the relative value in diagnosis of certain of the more classic symptoms and signs of hyperthyroidism. The criteria used are (a) the bedside data furnished by these symptoms and signs themselves as compared with (b) the basal metabolic rate and (c) the pathologic examination of the resected thyroid gland when this material is available.

The method consists of arbitrarily assigning the values shown to the following six symptoms and signs: nervousness, 1, tremor, 2, loss of weight, 3, tachycardia, 4, exophthalmos, 5 and goiter, 6, making a total of 21. By this means a numerical index of symptoms is arrived at which can be readily represented graphically on a chart showing the relation of the numerical index to the basal metabolic rate.

Nervousness is a subjective symptom, vague in its definition, characteristic of a wide variety of diseases and not quantitatively measurable.

Tremor is variable and except when typically fine, is not peculiar to hyperthyroidism.

The standard of loss of weight used in the study was 5 per cent or more of the recent normal weight of the patient.

By tachycardia is meant a pulse rate not falling below 90 under the conditions of the basal metabolic test.

The recognition of exophthalmos often involves the personal equation of the observer. If, however, a tendency is maintained to regard it absent unless positively present or plainly supported by other eye signs of hyperthyroidism, the sign is of high diagnostic significance.

The recognition of goiter is similarly involved. If the thyroid is appreciably enlarged, the degree of enlargement is of less significance as to the functional state than is the degree of vascular activity of the gland.

The cases studied number 147, taken consecutively without selection except to exclude those in which the patients had been recently treated with compound solution of iodine, by roentgen ray or by operation, presumably so as to modify the symptoms. The results are plotted in the chart. The symptom index is the base line, and the basal metabolic rate is the vertical.

* From the Medical Service of St. Luke's Hospital.

The great majority of those with a symptom index of 10 or less (102 cases) had a basal metabolic rate of less than plus 20, (one exception), and in only five of these 102 cases was the condition diagnosed as hyperthyroidism, though many of the patients had nontoxic goiter. On the other hand, all but four of the forty-five patients with an index of over 10 had a basal metabolic rate of more than plus 20, and

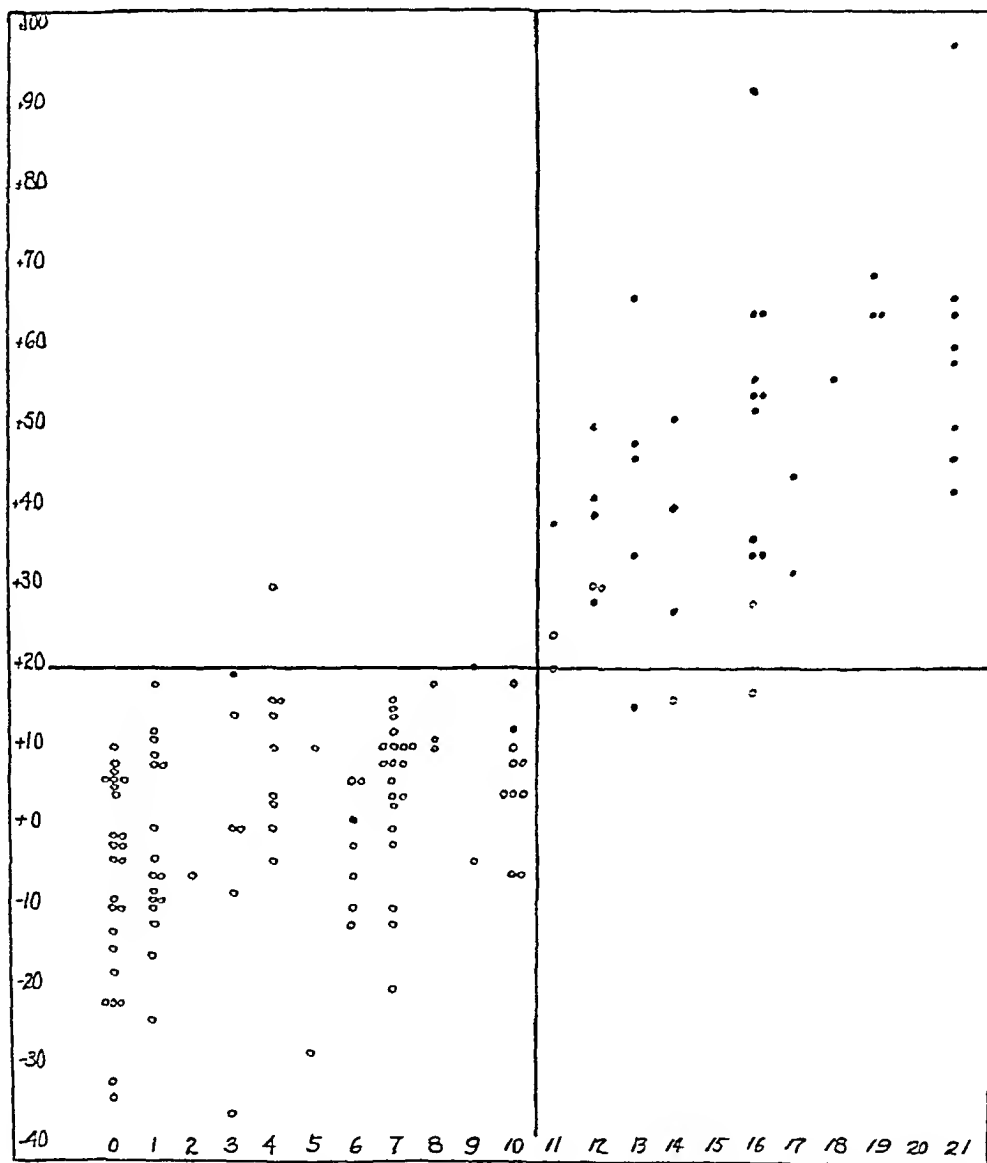


Chart showing relationship of the index of symptoms to the basal metabolic rate. The dark circles indicate the results for patients with exophthalmic goiter or toxic adenoma, and the light circles indicate the results for other subjects.

in all but four of these forty-one cases the condition was diagnosed as hyperthyroidism. The exceptions are briefly noted, and in some instances may be considered explained in the table.

The cases running according to rule fall in the southwest and northeast fields of the chart. With regard to the former there is

Data Relating to Cases Plotted in Chart Against the Rule, and to Case 11 in Which the Condition was Erroneously Diagnosed

| Field Case | Date | Name | Age | Sex | B | M | R | Index | N | Tr | L | Wt | Tach | Ex | G | Clinical Diagnosis | Thyroid ectomy | Pathologic Report | Remarks |
|------------|----------|------|-----|-----|------|---|---|-------|---|----|---|----|------|----|---|---|-------------------|--|---|
| N W 41 | 2/ 8/26 | I F | 48 | F | +30† | | | 4 | 1 | | 3 | | | | | Chronic Infectious tonsillitis | No | | Tonsils removed August, 1927, reported well Dec 17, 1927 |
| S W 1 | 12/16/25 | P P | 25 | F | +19 | | | 3* | 1 | 2 | 3 | 3 | 1 | | 6 | Duodenal ulcer, toxic adenoma Nontoxic adenoma | No | Adenoma in mild exophthalmic goiter | No further record |
| 2 | 12/17/25 | R S | 16 | F | +1 | | | 6 | | | | | | | 6 | | Yes | Simple goiter or normal thyroid | |
| 11 | 1/12/26 | W D | 27 | M | +11 | | | 8 | 1 | | 3 | 1 | | | | 1/12/26, not made 3/6/26, probable toxic goiter† | Yes | Toxic adenoma in exophthalmic goiter | |
| 68 | 3/16/26 | H F | 36 | F | +20 | | | 9* | 1 | 2 | ? | ? | | | 6 | Toxic adenoma in exophthalmic goiter | Yes | Borderline exoph thalmic goiter | |
| 129 | 9/18/26 | N J | 36 | F | +12 | | | 10 | 1 | | 3 | | | | 6 | Exophthalmic goiter | Yes | | |
| S E 49 | 2/11/26 | M B | 37 | F | +20 | | | 11 | 1 | | 1 | | | | 6 | Psychosis | No | | Later a suicide |
| 48 | 2/12/26 | L H | 43 | F | +15 | | | 13 | | | 3 | 1 | | | 6 | Toxic adenoma | Yes | Toxic adenoma | "Much colloid, some cal cium in the capsule and substance of adenoma" Consistent difference in the two eyes |
| 143 | 2/16/27 | R R | 30 | F | +16 | | | 14 | 1 | 2 | | | | † | 6 | Sympatricotonia | No | | Tricking compound solu tion of iodine for past six weeks |
| 76 | 3/26/26 | M W | 29 | F | +17 | | | 16 | 1 | 2 | 1 | | | | 6 | Colloid goiter | Yes | Colloid goiter, thyroiditis | No further records |
| N L 57 | 3/ 1/26 | S W | 50 | F | +24 | | | 11 | 1 | | | | | | 6 | Ovarian car cinoma | No | | |
| 69 | 3/17/26 | R M | 24 | F | +30† | | | 12 | 1 | 2 | 3 | | | | 6 | Chronic infectious tonsillitis | No | | |
| 136 | 10/ 6/26 | O O | 54 | F | +30† | | | 12 | 1 | 2 | 3 | | | | 6 | Nontoxic goiter | No | | 1, 2 and 8 improved in next few weeks |
| 59 | 3/ 2/26 | I T | 20 | F | +28 | | | 16 | 1 | 2 | 3 | 1 | | | 6 | Chronic infectious tonsillitis | No | | 12/17/27, reported still ner vous and toxic thyroid suspected |

† Considered erroneous

* Metabolism room record

† Bedside record

no subsequent record to indicate that any of the patients has subsequently become a recognized subject of toxic goiter. With regard to the northeast field, the condition in thirty-seven cases was diagnosed exophthalmic goiter or toxic adenoma. Most of these patients were subjected to operation and the thyroid tissue submitted for examination (thirty-one cases). The pathologic reports supported the clinical diagnosis in these thirty-one cases, whereas it did not in certain of the cases noted in the table.

The study suggests, as would be expected, that the diagnosis of hyperthyroidism approaches certainty as the index exceeds 10.

In the absence of exophthalmos and goiter (index 10 or less), hyperthyroidism was rarely found to exist even though nervousness, tremor, loss of weight and tachycardia were present.

When exophthalmos and goiter were present, other cardinal symptoms also occurred.

The absence of exophthalmos in toxic adenoma limits the total possibilities of the index in that condition, but the adenomatous goiter, if toxic, is usually associated with tachycardia and one or more of the other common symptoms.

The valuation suggested may occasionally serve as a useful check on erroneous acceptance or interpretation of the basal metabolism determination in the diagnosis of exophthalmic goiter and toxic thyroid adenoma.

THE EFFECT OF EMOTION ON BASAL METABOLISM *

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The results obtained by two of us (Strouse and Binswanger) ¹ from the therapeutic use of iodine in the treatment of patients for symptoms of the complex resembling hyperthyroidism without increased metabolism suggested the study of the relation between the nervous symptoms, metabolism and the use of iodine in hyperthyroidism ² To put this idea to experimental test involved a procedure which attempted to change the emotional state of a person and then to study the effect of such emotion on the metabolism We believed that for our purpose in a general hospital, a simple procedure applicable to all classes of patients would give results of comparative value Of course, we realized the improbability of evolving any standard test when dealing with emotion or of obtaining any constant emotional reaction to a given psychic stimulus To this end we decided to study in operative cases the effect of the knowledge of an impending operation on the basal metabolic rate, pulse rate, blood pressure and subjective emotional state

Three classes of patients were studied The first consisted of the usual operative cases, the second of a group of patients with hyperthyroidism who had received the present day preoperative iodine therapy, and the third, patients with hyperthyroidism who had not received iodine or only insignificant amounts After these patients had been in the hospital varying lengths of time, their basal metabolic rates were determined Another metabolism test was done the morning before and the morning of operation, the patient having been informed of the time of operation the preceding evening The pulse rate, blood pressure, respirations and emotional state were observed at the same time In a few cases the technic was slightly altered in that the patient was informed on the morning of operation just previous to the metabolic reading

* From the Thyroid Study Group and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital

1 Strouse, S, and Binswanger, H F Symptom Complex Resembling Hyperthyroidism Without Increased Metabolism, J A M A 88 161 (Jan 15) 1927

2 Hyperthyroidism is used throughout this paper as descriptive of a general group including all gradations from the typical exophthalmic goiter to the so-called adenomatous goiter with hyperthyroidism

The basal metabolism test was performed at the bedside, the portable Benedict-Roth apparatus being used. Computations were made from the Aub-Dubois tables. In some cases one, and in some two, six-minute periods were run. Conditions of the test were always the same: the patient was in bed all night, and received nothing by mouth after midnight. Sedatives were not administered the evening before or the morning of operation. The pulse rate was taken during the breathing period, and the blood pressure and temperature by mouth immediately following. Respiratory quotients were not determined.

RESULTS

GROUP 1—The first group consisted of twelve patients, eight males and four females, varying in age from 14 to 60 years. The basal metabolic rates were all within normal limits.

Only three of these patients showed any outward emotional manifestations on the morning of operation. The rate of metabolism of one of these rose 6.1 per cent (case 5), of the other two, one fell 4 per cent and one 13.4 per cent (cases 3 and 10). The pulse and blood pressure did not show any marked change. The remaining nine patients did not manifest demonstrable emotional reaction. Of these only one had an increase of 6.4 per cent, and this may be explained by an accompanying rise in temperature to 99.4 F. Either the others did not show any appreciable fluctuation or the metabolic rate decreased slightly. A constant relation did not exist between the pulse rate, blood pressure and metabolic rate. The respiration was not materially affected in any case.

GROUP 2—The second group comprised twelve patients with hyperthyroidism who had received the present day preoperative treatment with iodine. In all of these the administration of compound solution of iodine had improved the nervous symptoms and had considerably lowered the basal metabolic rate. In most cases compound solution of iodine (Lugol's solution), 10 minims (0.6 cc) three times a day, was administered for from six to twenty-five days. Two patients received 15 minims (0.92 cc) three times a day, and in some an additional 30 minims (1.9 cc) was given the night before operation. The patient in case 21 received syrup of hydriodic acid, 1 drachm (4 cc) three times a day for fourteen days, followed by compound solution of iodine, 10 minims three times a day for thirteen days.

Of the twelve patients in this group (table 2), only five (cases 13, 17, 21, 22 and 24) showed outward emotional disturbances (nervousness and great anxiety). The metabolic rate in cases 13 and 17 remained practically the same the morning of operation, although the pulse in the former rose from 12 to 24 beats per minute. The

metabolic rates in cases 21, 22 and 24 increased approximately 6 per cent. The pulse rate rose in all of these, whereas the blood pressure varied.

Of the remaining seven patients, three (cases 16, 20 and 23) did not show appreciable change the morning of operation. In the last

TABLE 1—*Data of Patients Not Having Thyroid Disease*

| Case | Age and Sex | Relation to Operation* | Basal Metabolic Rate | Pulse | Respiration | Blood Pressure | Comment † |
|------|-------------|---------------------------|-------------------------|-------------------------|----------------|----------------------------|--|
| 1 | 44 M | -1 0 0 ¹ | -12.6 -17.6 -21.9 | 60-64 55-64 56 | 17 16 16 | 108/80 110/80 | Hernia Informed of operation between 0 and 0 ¹ Told operation was to be performed |
| 2 | 33 M | -1 0 0 ¹ | +10.9 +4 +5 | 60-64 72-76 84 | 13 14 14 | 90/55 90/64 118/70 | Hernia Informed of operation between 0 and 0 ¹ |
| 3 | 60 M | -1 0 0 ¹ | -6.8 -8.7 -12.7 | 60 56-60 55-60 | 18 16 16 | 90/60 90/64 106/64 | Duodenal ulcer, vomiting, and emaciation Told he was to be operated on after 0 reading Appeared angry, desired to see his wife |
| 4 | 46 M | -1 0 | +1 -6.3 | 60 60 | 18 17 | 104/80 | Chronic osteomyelitis eight previous operations |
| 5 | 36 F | -1 0 +11 | -9.7 -3.6 -9.1 | 88-96 88-96 76-84 | 19 19 15 | 114/80 108/78 | Chronic appendicitis marked tremor Cried and was nervous morning of test |
| 6 | 52 M | -1 0 | -9.7 -8.1 | 53 52 | 9 9 | | Gastric ulcer |
| 7 | 36 M | -1 0 | -3.8 -5.2 | 48-52 50 | 15 15 | 90/45 108/60 | Duodenal ulcer |
| 8 | 46 F | -1 0 | +9.1 +7.5 | 52 56-60 | 16 22 | 118/70 108/60 | Appendix, lagophthalmos |
| 9 | 44 M | -1 0 | +3.8 +3 | 71 62-70 | 26 20 | 100/70 95/60 | Chronic intestinal obstruction Coarse tremor |
| 10 | 30 F | -3 -1 0 | +3.8 +5.2 -8.2 | 98-100 80-92 88 | 17 18 20 | 100/60 104/70 110/70 | Retrocecal appendix Did not sleep most of night |
| 11 | 37 M | -10 -7 0 | -9.2 -2.6 -10 | 58 52 56-58 | 12 12 11 | 130/80 124/70 110/65 | Cholecystotomy and appendectomy Up all night, pain in abdomen and shoulders |
| 12 | 14 F | -2 -1 0 | -3.4 -4.7 +1.7 | 68-72 68-72 80 | 10 9 9 | 114/58 108/60 | Appendectomy tremor, adolescent thyroid Temperature, 99.4 |

* In this table and in tables 2 and 3 0 indicates the morning of operation, 0¹ indicates that two tests were made on the day of operation one before the patient was told of the operation and one after being told. Other numerals state number of days before or after operation.

† The patients were notified the night before of the operation except when otherwise stated. Outward manifestation of emotion did not occur unless indicated in this column.

two, the pulse rate and systolic pressure showed moderate rises. The metabolic rates in cases 15 and 19 fell approximately 8 per cent, without any changes in the pulse rate. The marked fall of 18.8 per cent in case 14 suggests the possibility of some error. The changes in metabolic rate, pulse rate and blood pressure did not present any parallelism.

GROUP 3—As already stated, group 3 consisted of patients with hyperthyroidism who had not been iodized. It is limited to only six

patients because of some untoward reactions which occurred. To obtain the effects of the mode of procedure adopted in the other two groups, these patients were likewise informed the night before that operation was to take place the next morning. But after the metabolism test was made that morning, actual operation did not follow. They were then put on the present day preoperative course of iodine. Four of

TABLE 2—*Data of Patients with Thyroid Disease Treated with Compound Solution of Iodine*

| Case | Age and Sex | Relation to Operation | Basal Metabolic Rate | Pulse | Respiration | Blood Pressure | Amount of Iodine Received, Cc. | Comment |
|------|-------------|-----------------------|----------------------------------|--------------------------------|----------------------|---|--------------------------------|---|
| 13 | 40 F | -7 -1 0 | +35.5 +30.2 +31.6 | 100 92 104-114 | 26 21 20 | 120/50 | 32 | Nervous |
| 14 | 37 F | -1 0 | +47.4 +28.7 | 84-98 90-94 | 11 10 | 108/50 110/60 | 24 | Did not sleep well due to noise next door |
| 15 | 37 M | -7 -1 0 | +31.8 +29.9 +22.4 | 108 76 78-90 | 13 12 10 | 100/50 100/55 | 29 | |
| 16 | 22 F | -19 -1 0 | +56 +42.4 +39.7 | 124 104 | 24 18 21 | 138/62 | 40 | |
| 17 | 40 F | -1 0 | +35.1 +36.3 | 108-112 108-110 | 13 12 | 136/70 118/40 | 42 | Great anxiety |
| 18 | 48 F | -19 -1 0 +3 | +61.7 +39.2 +47.7 +42.7 | 116 96-104 100-108 88 | 21 20 19 18 | 144/80 140/80 110/60 | 13 | Temperature, 99 |
| 19 | 32 F | -11 -1 0 | +53.7 +23.7 +14.9 | 104 80-88 84 | 16 15 16 | 98/60 110/60 | 18 | |
| 20 | 29 F | -28 -1 0 | +40.8 +19 +19.7 | 132 100-104 120-130 | 15 16 15 | 100/40 125/40 | 34 | |
| 21 | 43 F | -35 -12 -1 0 | +56.7 +31.1 +29.1 +35.4 | 140-152 114 120-124 | 26 22 22 | 148/96 190/110 180/104 164/106 | 28 | { From April 19 to May 3, 1 drachm of syrup of hydriodic acid was given three times a day Worried a great deal |
| 22 | 32 F | -1 0 | +29.3 +34.5 | 88-94 104-114 | 21 17 | 104/60 124/0 | 22 | Showed anxiety |
| 23 | 34 M | -1 0 | +32.1 +33.3 | 98-98 120-128 | 24 25 | 138/70 150/70 | 31 | Temperature, 99.2 |
| 24 | 33 F | -1 0 | +37.6 +44.3 | 92-94 110-114 | 24 24 | 118/62 118/50 | 30 | Temperature, 99 excited |

these patients are also included in group 2, thus affording us the opportunity of studying them before and after iodine therapy.

The results obtained are discussed individually. The metabolic rate in case 14 rose from +43.1 per cent two days before operation to +77.7 per cent the morning of operation. The pulse rate and blood pressure remained constant. The metabolic rate in case 23 increased from +50.7 per cent to +75.8 per cent within a few minutes. The pulse rate and systolic blood pressure ascended slightly. This patient

was the only one of this group who had received any compound solution of iodine before this experiment. He had taken five drops three times a day for two weeks, and the metabolic tests were done seven days after iodine had been discontinued. In case 24 the metabolic rate the day before operation was +72.6 per cent, and the morning of supposed operation it was +97.2 per cent. Here again the pulse rate remained practically unchanged. The following day the rate of metabolism returned almost to its previous level. In case 25, the morning before supposed operation the metabolic rate was +47.6 and the morning of operation, +66.5 per cent. The pulse rate and blood pressure are of

TABLE 3—*Data of Patients with Hyperthyroidism Who Did Not Receive Compound Solution of Iodine*

| Case | Age and Sex | Relation to Operation | Basal Metabolic Rate | Pulse | Respiration | Blood Pressure | Temperature | Comment |
|------|-------------|---------------------------|---|--|--------------------------|--------------------------------------|------------------------------|--|
| 14 | 37 F | -2 0 | +43.1 +77.7 | 104 100-106 | 19 15 | 120/70 134/70 | | |
| 23 | 34 M | 0 0 ¹ | +50.7 +75.8 | 110-130 108-136 124-132 | 27 32 29 | 130/60 130/60 146/62 | | Informed of operation after reading of 0 |
| 24 | 32 F | -5 -1 0 +1 +2 | +77.9 +72.6 +97.2 +79.9 +83.6 | 116 124 120-132 124 124 | 29 20 21 22 | 130/0 | | Greatly excited |
| 25 | 58 M | -5 -1 0 +1 | +38.4 +47.6 +66.5 +35.6 | 100-104 Irreg 100-112 108-114 | 14 14 15 14 | 112/60 126/40 96/50 120/68 | 98.6 98 98 98 | |
| 22 | 32 F | -3 -1 0 +1 | +40.9 +41.6 +53.8 +52.5 | 114-116 120 | 18 19 19 | 146/60 70/80 148/60 | 90 90 99 | Greatly excited |
| 26 | 44 F | -1 0 +1 | +53.9 +182 +270 -63.4 | 114-122 116 150 168-112 | 20 21 17 20 | 140/80 150/50 164/70 140/60 | 98.6 98.6 100.2* 98 | Metabolism test repeated one hour later |

* Rectally

doubtful value, as fibrillation was present. In case 22 occurred the least increase, which was 12.2 per cent. On the following morning, the rate of metabolism had not returned to the level found before operation. The pulse rate was not recorded the morning operation was performed. The systolic blood pressure rose 44 mm and the diastolic, 20 mm. This patient and the one in case 24 both showed marked excitability on the morning of operation. In case 22, the maintenance of the same metabolic rate as that found the morning following operation is possibly due to the excitement brought on by the woman's reluctance in having this metabolic test performed. She had been instructed that no more tests were to be done.

Case 26 is remarkable in the reaction that occurred. On the morning before operation, the rate of metabolism was +53.9 per cent and within the range of previous determinations. On the morning of operation it reached the high level of +182 per cent, although the pulse rate remained about the same as that of the previous morning. Immediately following the metabolism test, the patient went into a state simulating acute thyroid intoxication. The pulse rate rose to 160, and the temperature to 100.2 rectally. Morphine sulphate, $\frac{1}{6}$ grain (11 mg) was administered hypodermically, and the metabolism test was repeated about one hour later. At this time the metabolic rate was +270 per cent, the pulse rate 150 and the temperature, 100.2 rectally. By afternoon the patient seemed to have made a good recovery. The following morning, the basal metabolic rate was +63.4 per cent, the pulse rate 110, and the temperature was normal.

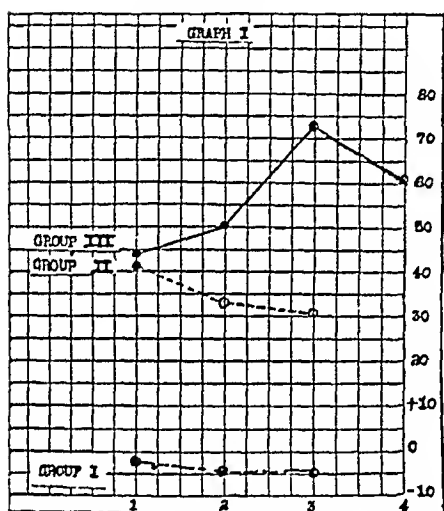


Figure 1

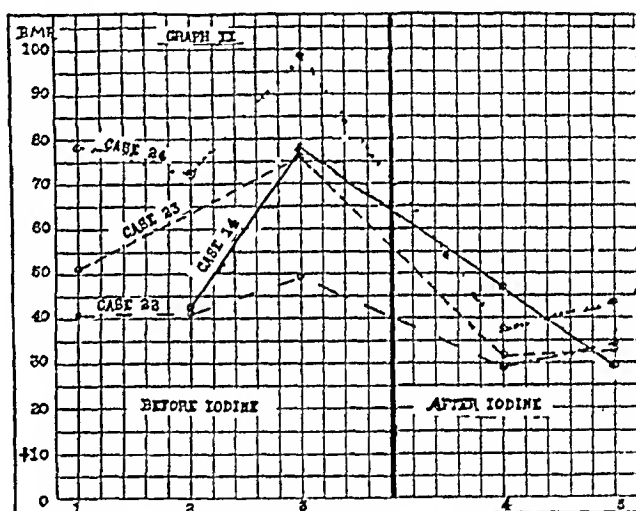


Figure 2

Graph I represents the average changes in metabolism in the various groups, while graph II shows the difference in metabolic rate obtained in the same patients by the same procedure after iodine therapy.

The average changes in metabolism in the various groups are represented in graph I of the accompanying chart. Graph II shows the difference in metabolic rate obtained in the same patients by the same procedure before and after iodine therapy.

COMMENT

In the literature various methods have been employed to demonstrate the effect of emotional reactions on metabolism. Necessarily numerous factors come into play which make results difficult to interpret. Grafe and Mayer³ performed a series of experiments on hypnotized

³ Grafe, E., and Mayer, L. Ueber den Einfluss der Affekte auf den Gesamtstoffwechsel, *Ztschr f d ges Neurol u Psychiat* 86:247, 1923.

persons, suggesting various calamities such as death of relatives, amputation of arms, etc. In nine such tests, there was an increase in metabolic rate ranging from 5 to 25 per cent. In four experiments no change or only a slight lowering of the rate occurred. From this the authors concluded that emotion may cause a definite increase in metabolism.

Ziegler and Levine,⁴ making tests on psychasthenic war veterans, found a marked rise in the metabolism as the result of emotion in eleven cases, in three they found a fall, and in one not any change. They produced emotional disturbance during the breathing periods, by having the veterans think of a disagreeable experience in the army. Crile⁵ stated that the metabolic rate falls in rabbits badly frightened by dogs. Landis⁶ reviewed the literature concerning the relationship between the metabolic rate and the emotional state of psychotic persons and found that an altered or emotional state does not necessarily affect the metabolic rate. In his experiments, anticipation of strong electrical stimulation raised the metabolism in three persons tested, 6, 17 and 37 per cent. He stated that emotional disturbance per se does not always produce the same change in the metabolic rate.

The question arises whether our procedure affected the emotional state. In all our patients outward indications of emotional reactions were not noted, but the significant fact is that the same mode of procedure in different groups of persons resulted in similar effects on the basal metabolism in two groups, and a totally different reaction in the third group. These results occurred whether or not subjective manifestations of emotional reactions were present. The basal metabolic rate of patients not having thyroid disease was not heightened by this procedure. The caloric output of the majority of patients with thyroid disease whose condition had been stabilized by iodine therapy was likewise not affected. In some, a slight rise occurred. The increase resulted in those patients with hyperthyroidism who had not received the present day iodine therapy.

With a similar procedure in patients with thyroid disease who had not received iodine, Segall and Means⁷ obtained a rise in the metabolic rate the morning of operation, but the average increase in their experiment was from 1 to 6 per cent. In our six cases the increase ranged

4 Ziegler, A. M., and Levine, B. S. The Influence of Emotional Reactions in Basal Metabolism, *Am J M Sc* **169** 68, 1925.

5 Crile, G. W. The Thyroid Gland, Philadelphia, W. B. Saunders Company, 1922.

6 Landis, C. Studies of Emotional Reactions—Metabolic Rate, *Am J Physiol* **74** 188, 1925.

7 Segall, H. N., and Means, J. H. The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter, *Arch Surg* **8** 176 (Jan.) 1924.

from 12.2 to 24.6 per cent the patient who had a profound reaction not being considered. It is possible that this difference in results is due to the fact that Segall and Means' patients received morphine sulphate, $\frac{1}{4}$ grain (16 mg.) hypodermically previous to the metabolism test.

What is the mechanism that produces the increase in metabolic rate in these patients with thyroid disease? Grafe³ believed that the rise of caloric output following emotion is caused by a general alteration in the organism as a result of stimuli from centers in the brain passing out to the periphery, chiefly by means of the sympathetic nervous system and also by some increase in the metabolism of the brain itself. Aub⁸ thought that the effect is due to epinephrine, the point of action being a direct one, in that it influences the metabolism by affecting the peripheral muscle tissue. Segall and Means also considered it an epinephrine response. The latter views fit in with Cannon's theory⁹ of epinephrine reaction to fright and fear. Our results in the patients of group 3 likewise suggest an increased production of epinephrine as the cause of the metabolic change, for in three of the four cases studied before and after the administration of iodine, the caloric output had dropped the following day. This could not be consistent with a thyroxin reaction, because thyroxin produces a reaction lasting days or even months. The increased heat production due to epinephrine is immediate and transient.

We are unable to state why such a marked reaction should occur in patients with hyperthyroidism who have not received compound solution of iodine as compared with those who have received sufficient iodine. Naturally this brings up the old question as to the mechanism that causes iodine to reduce, to a certain extent the nervous symptoms and metabolic rate in hyperthyroidism. We cannot say whether it fits in with Plummer's¹⁰ idea or the latest mechanical one of Marine,¹¹ who suggests that the enlargement of the vesicles produced by the increased colloid in the regression of the hyperplasia compresses the lymphatics and capillaries and thus lessens the absorption of thyroxin. Perhaps those patients with thyroid disease who had received iodine and who

8 Aub, J. C. The Relations of Internal Secretion to Metabolism, J. A. M. A. **79** 95 (July 8) 1922.

9 Cannon, W. B. Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton and Company, 1915.

10 Plummer, H. S. Results of Administering Iodine to Patients Having Exophthalmic Goiter, Society Proceedings, J. A. M. A. **80** 1955 (June 30) 1923.

11 Marine, D., Deutsch, M. and Cipra, A. Effect of Large Doses of Iodine in Heat Production in Rabbits, Proc. Soc. Exper. Biol. and Med. **24** 657 1927.

still had a slightly increased metabolic rate the morning of operation were markedly hyperplastic and sufficient iodine had not been administered

SUMMARY

1 The effects of the thought of impending operation on basal metabolic rate, blood pressure and pulse rate were studied in three groups of cases

(a) A constant effect on the rate of metabolism was not seen in group 1, which consisted of patients of various types of nervous stability with a normal rate of metabolism

(b) In group 2, which was made up of patients with hyperthyroidism who had received iodine according to present day preoperative routine, a marked rise in metabolic rate did not occur the day of operation

(c) Group 3 was comprised of persons with hyperthyroidism who had not had iodine, as in group 2. In these patients a marked increase in the basal metabolic rate resulted the morning of supposed operation

2 A practical point for consideration is the possibility of using the foregoing procedure as an index of complete or incomplete iodination. A rise of the metabolic rate the morning of operation might indicate that an insufficient amount of iodine had been given

SECOND INFECTION IN SYPHILIS

ITS RELATION TO THE TIME OF TREATMENT OF THE FIRST
INFECTION *

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It has long been recognized that second infections in syphilis in man are not common, indeed, prior to the discovery of spirochetes and the introduction of arsphenamine, a comparatively small number of supposed instances had been reported, and there was considerable discussion as to their actual occurrence. Ricord and Fournier stated that they had never observed a satisfactory example, whereas in 1895 Hutchinson reported fifty-four "reinfections," only a few of which his son later was willing to accept.

When the diagnosis of syphilis rested on clinical grounds alone, the recognition of the occurrence of second infection with this disease was admittedly difficult and frequently open to question. Many of the instances reported prior to 1910 may have been and doubtless were true examples of second infection, but since the diagnosis rests entirely on clinical grounds the evidence is hardly acceptable according to present standards. With the discovery of the causative agent of the disease, it was possible to place the identification of a second infection on a firmer footing, for now exact proof of the syphilitic nature of the suspected lesion can be adduced. In 1914, Benario collected from the literature ninety-six reported cases of "reinfections," in which the patients had first been treated with the recently introduced arsphenamine or with arsphenamine and mercury. He was concerned mainly with the superior curative properties of arsphenamine, as evidenced by the great number of "reinfections" reported within a few years. It is now generally accepted that second infections do occur, which may and usually do behave in all respects like first infections.

THE PROBLEM

As a result of his experiments on apes, Neisser came to the following conclusions in regard to syphilitic infection: radical cure of the disease can be effected by appropriate treatment, treated animals can be infected

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a second time under certain conditions, a successful second inoculation indicates the elimination of the first infection, failure of the second inoculation indicates the presence of a resistant state (immunity), the presence of this resistant state depends on the persistence of the first infection, without a persistent infection, there is no resistant state, and hence the demonstration that any particular treated animal is resistant to a second inoculation indicates the failure of treatment to bring about cure of the first infection in that animal. Until recently these conclusions have dominated the conception of acquired immunity in syphilis, both in man and animals. However, fresh evidence of an experimental nature has appeared which questions the validity of the idea that immunity in this disease is necessarily dependent on the presence of spirochetes in the tissues.

Brown and Pearce showed that in rabbits early nonsterilizing treatment (eighteen days after inoculation) rendered the animals susceptible to a second inoculation six days later with a homologous strain of the syphilitic virus. Kolle was the first to show experimentally that the time at which treatment is begun in the course of syphilitic infection exerts an important influence on the reaction to a second inoculation with the homologous strain of spirochetes. This investigator found that if syphilitic rabbits were treated within forty-five days after inoculation, they could almost invariably be infected a second time, whereas, if treatment were postponed until ninety days or more after the first inoculation, they were almost always resistant to a second inoculation with homologous strains of spirochetes. On the basis of Neisser's generalizations, Kolle concluded that the successful second infection of the rabbits treated early indicated that they had been cured, but that the rabbits treated late had not been cured, since they were refractory to a second inoculation. The experimental results of Kolle have been confirmed by Frei, Adachi and Chesney and Kemp. The last named workers found in addition that, no matter whether treatment was begun before the forty-fifth day or postponed until after the ninetieth day it was apparently effective in sterilizing the lymph nodes and internal organs of the rabbits. Their experiments suggested that the specific resistance which develops during the course of syphilitic infection may persist after the infection has been eliminated, and hence may not necessarily be dependent for its continued existence on the presence of spirochetes in the host. It is obvious that this conception of acquired immunity in syphilis is at odds with the conception formed by Neisser and generally held since his day.¹

1 For a complete discussion of the question of immunity and resistance in syphilis, see "Immunity in Syphilis" by A. M. Chesney.

If, as Neisser concluded, acquired immunity to syphilis is dependent on the persistence of the original infection, and if the present intensive method of treatment, regardless of the time at which it is begun, can bring about a complete cure, there should have occurred by now many second infections of syphilis in patients who came under treatment for the first time late in the course of the disease, provided always that many persons who have had syphilis are subsequently exposed to infection. Since 1910, many syphilitic patients have been given intensive treatment comparatively late in the course of the disease. Hence it is now possible to determine the relation of the time of treatment of patients with first infections to the incidence of second infections, and, as a corollary, to ascertain the proportion of second infections occurring in patients in whom treatment was begun late in the course of the disease. Such is our purpose in this communication.

SELECTION AND CRITERIA OF REPORTED INSTANCES OF SECOND INFECTION

We have reviewed the case reports in the literature since 1910 of examples of "reinfection," "superinfection" and "second infection," the last of which terms we prefer since it implies nothing in regard to the presence or absence of the first infection. Unfortunately, a few of these reports were in unavailable journals and do not appear in this collection, nor have we been able satisfactorily to tabulate many examples reported as a part of general studies of the results of treatment. Altogether we have reviewed the reports of cases of 676 patients with supposed second infections, to which are added eight instances from the syphilis clinic of the Johns Hopkins Hospital, which have not hitherto been reported in detail.

We have sought to determine whether or not all these instances could be regarded as examples of second syphilitic infection in accordance with criteria which we have adopted for the recognition of such a condition. We have two such criteria.

- 1 There must be proof that the patient had syphilis prior to the occurrence of the suspected second infection, and this proof must rest on the demonstration of spirochetes in a lesion or the occurrence of a positive Wassermann reaction in the blood serum, and not on clinical judgment alone.

- 2 After an interval following antisyphilitic treatment and at a site other than that of the primary lesion of the first infection, there must develop a lesion with the characteristics of a chancre in which spirochetes can be demonstrated.

These criteria are not as rigid as those formulated by Stokes, but we consider that they are adequate for the establishment of the existence

of a second infection. They are not based on clinical diagnosis alone. It would be more convincing if every patient suspected of having a second infection could have been allowed to go without treatment for a period of time sufficient to permit him to develop signs of secondary syphilis. Before the discovery of the causative agent of syphilis such a procedure was necessary to establish the validity of a second infection, but in our opinion that is no longer necessary, nor is it even desirable from the point of view of the patient himself or of society in general. It may not be amiss to point out that if too rigid criteria are adopted, statistical study of second infections in human syphilis will never be possible unless there is great improvement in the manner of reporting such instances.

In a few instances, we have been unable to adhere strictly to the criteria of a second infection, so far as the location of the second chancre was concerned, although such examples have been included in this study, because some of the reports fail to state the precise location of the suspected primary lesion of the second infection in relation to the site of the original chancre. This is, of course, regrettable but could not be helped. It will be obviated if in the future those reporting instances of suspected second infection will be more explicit on this point.

When the 676 case reports were studied in the light of the criteria already outlined, it became necessary to reject 447, either because the data were insufficient for the purposes of this study or because the supposed instances did not fulfil the proposed criteria. The remaining 229, which were deemed acceptable, together with the eight from this clinic, were studied with reference to the time at which treatment was begun during the course of the first infection, and also with reference to the interval between the beginning of the treatment and the onset of manifestations of the second infection. The data obtained from this study are presented in table 1 in summarized form.

In group A of this table are presented all those patients in whom the interval between the beginning of the first treatment and the second infection (or the appearance of the lesion of the second infection) was more than a year, and in group B, those patients in whom this interval was less than a year. This distinction has been made because it is thought that in treated syphilitic patients, relapses which take the form of primary or secondary lesions, and hence might be mistaken for second infections, are most apt to occur within the first year of observation. If this is true, those patients designated as group A are more likely to be true instances of second infection than those in group B.

Consideration of this table shows that of the 237 reported instances regarded as acceptable, 232 or 97.8 per cent of the patients received

active treatment early in the course of the first infection, that is to say, during the primary stage of the condition or before the secondary lesions had disappeared. Of these, 165 were treated in the primary and 67 in the secondary stage. There were only 4 patients in whom treatment was begun in the latent stage, and in whom there was subsequently good ground for believing that a second infection had occurred. There was one patient with undoubted evidence of congenital syphilis who acquired a second infection. Not a single instance could be found of

TABLE 1—*Patients with Second Infection Showing Stage of First Infection at Time of Treatment*

| Stage | Group A | Group B | Total A and B | Per Cent |
|--|---------|---------|---------------|----------|
| Primary duration and serology unknown | 7 | 13 | 20 | 8.4 |
| Primary seronegative, duration unknown | 21 | 16 | 37 | 15.6 |
| Primary seropositive duration unknown | 25 | 17 | 40 | 16.8 |
| Primary duration known serology unknown | 9 | 2 | 11 | 4.6 |
| Primary duration known serology negative | 20 | 13 | 33 | 13.9 |
| Primary duration known serology positive | 16 | 8 | 24 | 10.1 |
| Total Primary | 93 | 69 | 165 | 69.4 |
| Secondary duration known | 9 | 4 | 13 | 5.4 |
| Secondary duration unknown | 34 | 20 | 54 | 22.7 |
| Total Secondary | 43 | 24 | 67 | 28.1 |
| Total Primary and Secondary | 136 | 93 | 232 | 97.5 |
| Latent | 4 | 0 | 4 | 1.6 |
| Congenital | 1 | 0 | 1 | 0.4 |
| | 141 | 93 | 237 | 100.0 |

TABLE 2—*Patients with Second Infection Showing Duration of First Infection Before Treatment*

| Weeks | 1-2 | 2-3 | 3-4 | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 | 9-10 | 10-11 | 11-12 | 12-13 | 13-14 | 14-15 | 15-16 |
|-------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|------|-------|-------|-------|-------|-------|-------|
| Primary serology unknown | 1 | 2 | 4 | 1 | 2 | 1 | | | | | | | | | |
| Primary seronegative | 2 | 10 | 10 | 2 | 4 | 1 | | | 1 | | | | | | |
| Primary seropositive | 1 | 2 | 3 | 1 | 5 | 6 | 2 | 2 | | | 1 | 5 | | 1 | 1 |
| Secondary | | | 1 | 1 | | 1 | 1 | 1 | | | 1 | 5 | | 1 | 1 |
| Total (Eighty-three patients) | 6 | 14 | 18 | 5 | 12 | 9 | 3 | 3 | | | 2 | 5 | | 2 | 2 |

a second infection in a patient whose treatment was started when tertiary lesions were present.

More precise information as to the duration of the first infection before treatment was begun, reckoned from the date of exposure, was available in eighty-three instances. This information is summarized in table 2.

This table shows clearly that in man the number of instances of second infection of syphilis diminishes as the interval between the onset of the infection and the initiation of treatment increases. The same phenomenon also occurs in experimental syphilis in rabbits, pro-

vided that a homologous strain of spirochetes is used for the second inoculation The parallelism of the conditions obtaining in man and in the rabbit is pointed out more clearly in table 3

In each species there is observed a progressive diminution in the incidence of second infections when the time elapsing between the onset of the disease and the institution of treatment increases

TREATMENT

All the patients included in this series were treated during the first infection with arsphenamine, either alone or in combination with other drugs, except that one patient received mercury only another a proprietary arsenical product only, and a third bismuth only

TABLE 3—*Second Infections in Rabbits and Man*

| | Duration of First Infection Before Treatment | | | | | | | | |
|---|--|----------|------|---|----------|------|-----------------------------------|----------|------|
| | To Forty Six Days | | | Forty-Six to Ninety-One Days | | | Ninety-One — Days | | |
| | Total | Positive | Per | Total | Positive | Per | Total | Positive | Per |
| | Number | | Cent | Number | | Cent | Number | | Cent |
| Second in oculations in rabbits * | 85 | 73 | 85.8 | 95 | 34 | 35.7 | 148 | 7 | 4.7 |
| Second infec- tions in man | to Forty three Days Forty-six Patients | | | Forty three to Ninety Two Days Thirty three Patients | | | Ninety two — Days Two Patients | | |

*In obtaining data for rabbits material has been taken from papers by the following investigators Kolle, Chesnev and Kemp, Chesnev, Haller and Kemp, and Adachi

THE RARITY OF SECOND INFECTIONS IN WOMEN

It is striking that of the 237 instances of second infection included in this paper only 8 or 3.3 per cent, occurred in women Several possible explanations for this comparatively low incidence among women in our series suggest themselves It can scarcely be due to the relative incidence of syphilis in the two sexes, for, while the disease is probably more common in men, it is not twenty-eight times as frequent as in women A partial explanation may be found in the well known tendency of syphilis to run a silent course in women, often being detected only by the occurrence of a positive blood Wassermann reaction Such patients, numerous in any large syphilis clinic, are apt to come under treatment comparatively late in the course of the infection and as our study has already shown, the incidence of second infections under these circumstances is extremely low Possibly, also the infrequency with which careful vaginal examinations are made in women in whom a positive Wassermann reaction is detected may play an important rôle in that instances of second infection with chancres on the internal genitalia are overlooked

RECURRENT LESIONS AND THIRD INFECTIONS

There were recurrent lesions, usually of secondary type, during the first infection in seventeen patients, all of whom were further treated. In compiling our tables we classed these according to the stage of the recurrent lesions. These patients show that even with recurrent lesions, immunity may not develop to an extent sufficient to prevent a subsequent second infection.

There are in this series eight patients in whom third infections with syphilis occurred, in accordance with the criteria of this study. They afford evidence that third infections actually do occur, and further support the conclusion that if the patient is treated early, little if any immunity against subsequent infection develops.

SECOND INFECTIONS IN PATIENTS WITH VARIOUS TYPES OF SYPHILIS

Second Infections in Patients with Congenital Syphilis—Only the report by Tashiro of the case of a 25 year old man has been accepted as an instance of second infection occurring in a patient with stigmas of congenital syphilis. Other supposed examples have been reported by Arning, Doucy and Joltrain, Gaston, Gaucher, Gougerot and Guggenheim (two patients), Goizet, Hudelo and Jolivet, Roederer and Camus, Stern, and Suggett (two patients). Arning's case was considered doubtful, because it was felt that the diagnosis of congenital syphilis was made on inadequate evidence, the patient, who had hutchinsonian teeth developed on the lower lip a chancre which contained spirochetes. It seems questionable that the occurrence of hutchinsonian teeth alone (with no report as to the Wassermann reaction) can be accepted as certain evidence of a preexisting congenital syphilis. The other cases were deemed unacceptable, because the diagnosis was uncertain as regards either the congenital or the acquired infection.

Second Infections in Patients with Evidence of Syphilis of the Central Nervous System—The following authors have reported patients who are supposed to have acquired a second infection with, either previously or concomitantly, suggestive evidence of syphilis of the central nervous system, Brandt, Brandweiner, Fiocco, Friedlander (two patients), Gennerich and Zimmern, Lambior (three patients), Pohlman, Stumpke, and Zieler. Not one of these cases has been deemed acceptable for this study, because the diagnosis of one or the other of the two conditions is open to question, although in one of Friedlander's patients a diagnosis of tabes (without a report of the spinal fluid) had been made several years before the patient developed a penile lesion which contained spirochetes.

Second Infections in Patients with Cardiovascular Syphilis—Possible or certain recently acquired syphilitic infection in patients having more or less definite evidence of aortitis or aneurysm, resulting from a supposed previous syphilitic infection, has been reported by Conrad, Fischer, Oro, and Zak, but after critical study not one of these cases has been considered acceptable for this paper

COMMENT

This review of the instances reported in the literature since 1910 as examples of second infection with syphilis discloses that many of these must be regarded as doubtful, in the absence of more precise data. Of the 676 case reports studied, only 229 proved wholly acceptable according to the standards outlined. If these represent true instances of second infection in syphilis, then certain facts can be deduced from this study.

First, a remarkable parallelism is apparent, so far as the relation of the time of treatment of the first infection is concerned, between the results of reinoculation experiments in treated syphilitic rabbits and the occurrence of second infections in human beings treated for syphilis. In each species there is observed a lessened tendency toward the occurrence of second infections when a longer interval ensues between the occurrence of the infection and the beginning of treatment.

Second, in the overwhelming majority of instances regarded as second infections (97.8 per cent) the patients came under treatment for their first infection during the early stage of the disease, that is to say, before the period of secondary manifestations had elapsed. A slightly greater number of patients were first treated during the seronegative primary stage than during the seropositive primary stage (70 as compared with 64). A much greater number were first treated during the primary stage than during the secondary stage (165 as compared with 67). These differences suggest an increasing resistance on the part of the patient, in the absence of any precise data as to the relative frequency of primary and secondary syphilis in patients presenting themselves for treatment at a syphilis clinic. It is almost impossible to obtain any accurate figures as to the percentage of patients first seen in the seronegative or seropositive primary and early secondary stages, since these vary greatly according to the type of clinic (e.g., Gennerich and Zimmern working with patients in the German navy, see the lesions early), the character of the patients, and other factors, but on the average, the number of patients in the primary stage who seek admission to a clinic will probably be considerably less than that in the secondary stage, while of those with primary lesions the greater number will probably be seen for the first time when the Wassermann reaction has become positive. Yet there were over $2\frac{1}{2}$ times as many

patients with second infections in whom treatment was begun during the primary stage as there were those in whom treatment was begun after secondary lesions had appeared. The almost complete absence of second infections in patients who had latent syphilis at the time treatment was begun is striking, as well as the complete absence from this series of patients with tertiary lesions. Is this difference in the percentage of second infections in patients with syphilis who are treated early and those who are treated late to be explained on the basis of a greater number of cases of syphilis in which the patients come under treatment in the early stage of the disease than later?

A survey, shortly to be published, of all patients admitted to this clinic during seven years from 1920 to 1926 inclusive, reveals that of 8,064 new patients, 1,898 were first treated during the primary and secondary stages, that is, early, 3,895 were treated during the late stages, in the remaining number, the condition was undiagnosed or diagnosed nonsyphilitic, or the stage of the disease was not determined because of insufficient observation. The ratio of patients with early and late syphilis (1,898 as compared with 3,895) is thus almost exactly 1:2. Yet, as revealed by this paper, second infections occur in patients treated early as compared to those treated late in the ratio of 232:5 or 46:1. In other words, approximately twice as many patients are treated for the first time late in the course of the disease as are those treated early, yet second infections occur forty-six times more often in the latter than in the former group.

Is the difference to be explained on the assumption that postponement of treatment until late in the course of the disease fails to bring about radical cure and hence leaves the person still infected and perhaps immune to a second infection? It is almost universally admitted that it is much more difficult to cure patients who have syphilis when treatment is begun late than when it is begun early, especially if extensive disease of the internal organs has developed, but it is at least conceivable that patients with a long-standing infection without such extensive visceral involvement may be cured even if treatment is begun late. At present we do not know of any adequate clinical studies on this point.

Another possibility that might explain the difference in the percentage of second infections in patients treated early, as opposed to those treated late, is that patients who have reached the late stage of syphilis before being treated are not so apt to be exposed to second infections as are those who have come under treatment early in the course of the disease. The former are apt to be older, and their social relationships different (marriage, better economic circumstances) from those of the latter and of a sort making for less exposure to

syphilitic infection While this explanation can be neither dismissed nor proved, it has much less weight when considered in connection with those races in which syphilis is most prevalent, for in them exposure to syphilis begins relatively early in adolescence and often continues in spite of matrimony

It is clear that the great infrequency of second infections of syphilis in patients coming under treatment late in the course of their first infection can also be explained on the basis of an acquired immunity which persists in the absence of the first infection, that is, after treatment has effected a cure There is some experimental basis for this view Whether or not it is the correct explanation is impossible to say, but this much can be said, that if there were no such thing as acquired immunity to syphilitic infection persisting in the absence of the infection, and if modern treatment were effective in eradicating the disease, then, assuming that repeated exposure to infection occurs, one should be able to assemble a significant series of instances of second infection with syphilis in which treatment for the first infection was not undertaken until late in the course of the disease It has not proved possible to assemble such a series So far as this study goes, then, it is not in disharmony with the conception of an acquired immunity to syphilis persisting in the absence of infection On the other hand, it cannot be said to prove the correctness of that conception The results of this study might also be taken to indicate that treatment fails to cure patients in the late stages of syphilis, or that persons who have once had syphilis and have been treated for it are not thereafter exposed to syphilitic infection to anything like the extent they formerly were As to which explanation is correct, the future may decide

SUMMARY AND CONCLUSIONS

1 A statistical study has been made of the cases reported in the literature since 1910 as examples of "reinfection," "superinfection" or second infection in syphilis

2 Of the 676 cases reported, 447 have been considered to be unacceptable in accordance with the criteria outlined in the test These unacceptable cases are listed with the references in the second part of the bibliography

3 Two hundred and twenty-nine cases reported in the literature have been deemed acceptable, and to these have been added eight observed in the Syphilis Clinic of the Johns Hopkins Hospital, making a total of 237 patients

4 Two hundred and thirty-two, or 97.8 per cent, of these patients were treated for the first infection during the primary or secondary stage

5 Second infections occurred in four patients, or 1.6 per cent, who had had syphilis in a latent or late form (as evidenced by a positive Wassermann reaction without other signs indicating a primary or secondary stage) at the time they were first treated for the disease.

6 A second infection occurred in one patient, or 0.4 per cent, who presented undoubted evidence of congenital syphilis.

7 For the reasons previously discussed, second infections are expected to be, and are actually found to be, extremely rare in women.

8 There was not a single undoubted instance of a second infection in a patient who had, previously or concomitantly, had syphilis either of the central nervous system or of the heart and aorta.

9 The duration of the infection before the first treatment is known in 83 of the 232 patients who were first treated in the primary or secondary stage. It would indicate that virtually all were first treated before the end of sixteen weeks, and about 82 per cent before the end of eight weeks.

10 A close parallelism was observed, in man and in rabbits, between the relation of the time of treatment of the first infection and the incidence of second infections.

11 The relative frequency of a second attack of syphilis in patients who had been treated early for the first infection, as compared with the infrequency of second attacks in patients whose first infection had progressed to a latent or late stage before treatment indicates that the time of treatment for the first infection has an important bearing on the patient's acquired resistance to a second infection. It is pointed out that the relative infrequency of second infections in patients whose treatment had been begun late in the course of the disease is not in disharmony with the conception that acquired immunity to syphilis may persist in the absence of syphilitic infection.

REPORT OF CASES OF SECOND INFECTION WITH SYPHILIS AND ONE OF THIRD INFECTION

CASE 1—*First Infection*—A negro, born in 1892, had had lesions for several days when, on Dec 19, 1921, an indurated ulcer appeared on the glans and several similar ulcers on the prepuce. Spirochetes were not demonstrated, and the Wassermann reaction was negative. During the next eight days, the patient received 49 cc of tartar emetic, and the lesions healed rapidly.

On Jan 13, 1922, after a genital lesion had been present for three days and a rash for two days, the patient had a sparse maculopapular syphilid, erosive lesions on the lips, papulo-erosive lesions on the uvula and serpiginous papulo-erosive lesions on the prepuce. From Jan 13 to Dec 22, 1922, the patient received irregular treatment, totaling fourteen injections of flumerin (which was being investigated clinically at this time) and five injections of arsphenamine, twenty Wassermann reactions were negative. On Dec 7, 1922, the spinal fluid showed 7 cells, the globulin test was doubtful, and the mastic reaction was 4321000000.

On May 23, 1923, the patient returned after lesions had been present for three days. He had numerous papulo-erosive lesions on the glans, corona and shaft and a bilateral inguinal adenitis. Spirochetes were demonstrated. From May 23, 1923, to Jan 29, 1924, the treatment was irregular, totaling eighteen injections of arsphenamine and mercurial inunctions and potassium iodide for six weeks. Fifteen Wassermann reactions were negative, as was the Wassermann test of the spinal fluid, on Nov 11, 1924. On Dec 5, 1924, physical examination revealed small, irregular, sluggish pupils, palpable epitrochlear glands and a sluggish right achilles' reflex.

Second Infection—On Dec 18, 1925, at another clinic, two penile "warts" were fulgurated, one disappeared, the other persisted. On December 28, the Wassermann reaction was positive. On Jan 15, 1926, after the lesions had been present for four months, the patient had an elevated indurated lesion "as hard as cartilage" on the inner prepuce. Spirochetes were demonstrated. Treatment was given elsewhere.

CASE 2—First Infection—A white man, born in 1900, on Feb 20, 1924, about twenty-eight days after exposure, noticed a painless genital lesion. A friend exposed to the same contact also acquired a genital lesion. On April 7, the Wassermann reaction was doubtful. On April 9, there was visible on the shaft of the penis a crusted ulcer with an indurated reddish base, and on the right side of the glans a superficial nonindurated lesion, there was also a bilateral inguinal adenitis. Spirochetes were not demonstrated, but serum from the lesion on the shaft gave a positive Wassermann reaction. From April 11 to August 6, the patient received twenty-six injections of arsphenamine and four courses of mercurial inunctions and potassium iodide, each course extending from four to sixteen weeks. To October 5, twenty-four Wassermann reactions were negative, as was the spinal fluid on June 13. Later the patient was in a sanatorium for six months because of a condition diagnosed as pulmonary tuberculosis.

Second Infection—On December 17, after the lesions had been present for ten days, there appeared a small eroded indurated lesion in the coronal sulcus, without inguinal adenitis. Spirochetes were demonstrated, the Wassermann reaction was negative. The patient received treatment elsewhere.

CASE 3—First Infection—A white man, born in 1897, on Oct 23, 1919, after lesions had been present for five days, presented three clean ulcers on the penis, a bilateral inguinal adenitis and a palpable left epitrochlear gland. Spirochetes were demonstrated. From October 24 to November 14, he received four injections of arsphenamine, and then left the clinic. Four Wassermann reactions were negative.

Second Infection—On Jan 21, 1921, after a lesion had been present for about two weeks, the patient had a round, indurated, ulcerated, "typical" lesion on the left side of the corona and a left inguinal adenitis. Spirochetes were demonstrated. On January 24, the Wassermann reaction was positive. From January 25 to March 1, the patient received six injections of arsphenamine, the first two Wassermann reactions were positive, the next three doubtful and the last negative. On March 10, the spinal fluid was normal. The patient did not return for further treatment.

CASE 4—First Infection—A white man, born in 1894, about Oct 22, 1924, noticed several penile lesions, and several more appeared three days later. On November 2, he was supposed to have received an injection of arsphenamine from an outside physician. When he was in this clinic, on November 5, there were several shallow ulcers on the corona, one with a rolled edge and a parchment-

like base, and a bilateral inguinal adenitis. Spirochetes were demonstrated. From November 5 to December 11, the patient received irregular treatment, totaling eighteen injections of arsphenamine and twelve injections of bismuth. The first Wassermann reaction was suggestively positive, but sixteen subsequent tests were negative, as was the spinal fluid on September 26. The patient did not return to the clinic after December, 1925.

Second Infection—On Sept. 1, 1926, after the lesion had been present for seven days, there was an indurated ulcer on the inner prepuce and a bilateral inguinal adenitis. Spirochetes were demonstrated. From September 1 to October 21, the patient received five injections of arsphenamine. Four Wassermann reactions were negative. He was then treated elsewhere.

CASE 5—First Infection—A white man, born in 1892, was first seen on Dec. 4, 1914. Six weeks before (about six weeks after exposure) there had been a penile lesion, three weeks before, an eruption developed on the back, face and knees, three days before, sores appeared in the mouth. Examination revealed a pharyngitis, a mucous patch on the left anterior pillar, a maculopapular eruption on the back, buttocks and extensor surfaces of the arms, an enlarged left epitrochlear gland, the remains of buboes and a scar on the inner prepuce. The patient received arsphenamine, 0.5 Gm., on December 4, 0.3 Gm. each on December 12 and 22, and 0.3 Gm. on Jan. 2, 1915, he did not return for further treatment. The Wassermann reaction was positive on December 4 and 13, negative on December 22, and doubtful on Jan. 2, 1915.

Second Infection—The patient was next seen on Aug. 13, 1923. He had married in 1919, and his wife had had one healthy child and no miscarriages. For five days there had been a lesion, which had appeared about three weeks after exposure. Examination revealed on the mucous surface of the prepuce a clean, oval, indurated ulcer, covered with a yellowish-gray membrane, the base showed tiny red dots which represented thrombosed capillaries, there was also a general adenitis. Spirochetes were demonstrated, and the Wassermann reaction was positive. The patient received arsphenamine on the day of examination but did not return for further treatment.

Third Infection—The patient was next seen on June 10, 1927. Since his last treatment, he had not received further therapy, and recently he had had many exposures. Five days before, a small lesion had appeared on the shaft. On the left side of the shaft in the mid portion, examination showed a round, indurated lesion, with a thin crust, exuding clear serum, in which spirochetes were demonstrated. There was a bilateral inguinal adenitis, the left epitrochlear was about the size of a small pea. Physical examination otherwise was negative. On the same day, the blood Wassermann reaction was negative, as was the spinal fluid (globulin test, 0, Wassermann reaction negative, mastic test, 0000000000).

CASE 6—First Infection—A white man, born in 1899, was exposed about May 12, 1922. On July 7, after lesions and enlarged glands had been present for six days, there appeared a round, painless, indurated ulcer on the inner prepuce, and a general adenitis was also present. Spirochetes were demonstrated. From July 7 to August 25, the patient received eight injections of arsphenamine, the second Wassermann reaction was suggestively positive, the other seven negative. The patient then did not come for further treatment until October 23, when the spinal fluid was negative. On November 4, the patient began a course of mercurialunctions and potassium iodide.

Second Infection—On Nov 14, 1922, after a lesion had been present for about ten days, two recent and one indurated lesion were visible in the sulcus. Spirochetes were demonstrated. On November 15, the Wassermann reaction was negative, on November 18, doubtful. From November 22 to December 27, the patient received six injections of arsphenamine. Four Wassermann reactions were positive and two negative. He then left the clinic.

CASE 7—First Infection—After a white man, born in 1894, had had gonorrhea and had received some intramuscular injections, he was seen elsewhere on April 30, 1919, with a general adenitis and a negative Wassermann reaction. On July 21, examination showed several penile lesions, which had been present for six weeks. Spirochetes were demonstrated, and the Wassermann reaction was positive. On July 28, there were scattered papules on the trunk, moist lesions on the glans and prepuce, a papulo-erosive lesion on the lip, general adenitis and alopecia. From July 28 to September 8, he received six injections of the meta-hydroxyanilid of arsenophenyglycin (which was being investigated clinically at this time), five Wassermann reactions were positive and one doubtful. After receiving mercurial injections and potassium iodide for several weeks, the patient left the clinic. Three years later, on July 22 and Sept 26, 1922, the Wassermann reaction was negative.

Second Infection—On Jan 16, 1923, there was a small penile lesion in which spirochetes could not be demonstrated, the Wassermann reaction was negative. On January 20, the lesion was indurated, but again spirochetes could not be demonstrated. On January 22, an indurated, painless, "typical" lesion on the prepuce, and bilateral inguinal adenitis were present. Spirochetes were demonstrated and the Wassermann reaction was negative. On January 24 and 31 and on February 7, the patient received injections of tryparsamide, then, because the lesion was increasing in size, the Wassermann reaction had become positive and spirochetes persisted, arsphenamine was administered, totaling eight injections to April 3. Of the eight Wassermann reactions during these injections, the first two were positive, the next two doubtful and the last four negative. After April 3, the treatment consisted of mercurial injections and potassium iodide for several weeks. On April 27, the spinal fluid was negative. The patient disappeared from the clinic without further treatment.

CASE 8—First Infection—A negro, born in 1891, had had headaches for three weeks, an eruption for one week, sore throat for three days and some loss of hair. On Aug 31, 1921, an examination revealed an extensive eruption (macular, papular, pustular and follicular) in all stages, frambesiform lesions on the scalp, moist papules on the scrotum, urethritis, phimosis, an indurated nodule under the prepuce, an ulcerated syphilid on each tonsil and a general adenitis. From September 3 to October 26, he received eight injections of arsphenamine and then left the clinic. Of the Wassermann reactions, the first two were positive, the next doubtful and the remaining five negative. The patient returned to the clinic and received four injections of arsphenamine from Feb 8 to March 28, 1922, the first Wassermann reaction was doubtful, the next positive, and the last two negative. He again discontinued treatment.

Second Infection—On July 3, 1923, the Wassermann reaction was negative. On July 7, after a lesion had been present for about a week, the patient had a large, irregular ulcer involving the edge of, and extending under, the prepuce and on the glans. Spirochetes were demonstrated. On July 26, after an eruption had been present for three days, there was visible a large, flat, indurated pustular rash. Spirochetes were demonstrated in one of these lesions, on the same day, the spinal fluid was negative. From July 26, 1923, to Aug 6, 1924,

the patient received nineteen injections of arsphenamine and had two courses of mercurialunctions and potassium iodide, each course extending over six to eight weeks. Of the sixteen Wassermann reactions during this time, the first five were positive and the remaining eleven negative. The patient discontinued the clinic treatment.

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PANCREATIC FUNCTION AND UPPER INTESTINAL DIGESTION

A NEW METHOD OF STUDY *

SANFORD M ROSENTHAL, M D

MONTREAL

The methods at present available for determining the activity of the external pancreatic secretion are based chiefly on the estimation of the enzyme concentration of the duodenal contents and the presence of fat and starches in the stools. Such methods are helpful in advanced disease, but wide normal variations detract from their usefulness in earlier diagnosis and discourage their employment in laboratory experimentation.

The method which I have evolved is based on the estimation of the digestion of starch in the upper intestine. This is accomplished by giving starch by mouth, and studying the rate at which it is broken down by following the rise in blood sugar.

Traces of diastatic ferments are present in most body fluids, but they are produced in quantity only by the salivary glands and pancreas. Hahn and Meyer¹ found that the amylase from these two sources has similar enzymatic properties. Its activity is dependent on the hydrogen ion concentration of the medium. Willstatter² found the activity greatest at p_{H} 6.8, and Sherman³ has shown that it is entirely inhibited at p_{H} 4 on the acid side and p_{H} 10 to 11 on the alkaline side.

It is thus possible by administering the starch in a slightly acid solution to do away with any salivary digestion, and digestion will not begin until the acid gastric contents are neutralized in the small intestine. If the salivary enzyme is permanently destroyed by the acid and by its sojourn in the stomach, hydrolysis of the starch will depend almost entirely on pancreatic activity, and on the degree to which the medium in the upper intestine favors the working of the amylase. That these factors are constant in the normal is shown by the uniformity of blood sugar curves following the ingestion of starch by the normal person. Maclean,⁴ Gray,⁵ and Rowe and Rogers⁶ studied

* From the University Clinic, Royal Victoria Hospital

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the blood sugar after the feeding of starch, with particular reference to carbohydrate tolerance, and obtained uniform curves. Maclean found curves almost identical with those in which equivalent quantities of dextrose were administered. These investigators did not attempt to eliminate salivary digestion. That the intestinal absorption of dextrose is a fairly constant factor is shown by the uniformity in results of dextrose tolerance tests, so widely employed clinically in recent years.

METHOD

Rabbits were employed in the experiments. After a preliminary starvation of 16 to 24 hours, ten grams of uncooked soluble starch (Merck) were given in suspension in 50 cc of warm water, to which 0.2 or 0.3 cc of normal hydrochloric acid was added just before administration. This was given by stomach

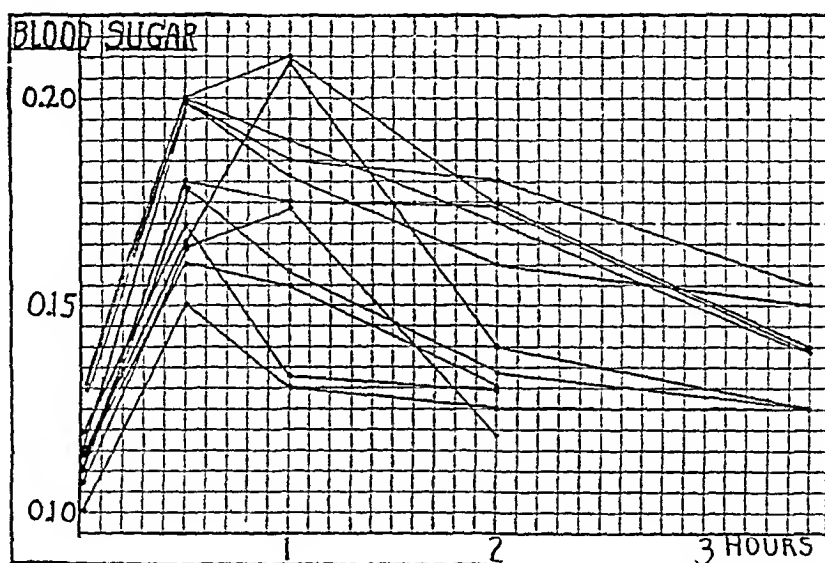


Chart 1—Blood sugar curves after the administration of 10 Gm of starch to normal rabbits

tube and washed in with 10 cc of water. Samples of blood were taken from an ear vein before and at intervals following the starch feeding, and the blood sugar was estimated by the method of Folin and Wu.

After normal curves were obtained in a series of rabbits, the pancreatic ducts were ligated. Then the tests were repeated after the rabbits recovered from the operation. There is usually only one pancreatic duct in the rabbit, and it enters the duodenum far down, 8 or more inches (20.3 cm) from the pylorus.

RESULTS

In a series of normal rabbits curves typical of sugar tolerance tests were obtained. The rises in blood sugar varied from 50 to 95 mg per hundred cubic centimeters of blood with an average of 62 mg per hundred cubic centimeters of blood. The blood sugar rose rapidly, usually reaching a maximum in one half hour, and then gradu-

ally falling, not quite to normal, within three and one half hours. In two rabbits to which acid was not given with the starch, the blood sugar curves were similar to the others in which 0.2 or 0.3 cc of normal acid was used.

TABLE 1—*Blood Sugar Changes after Administration by Stomach Tube of Ten Grams of Uncooked Starch in Fifty Cubic Centimeters of Water to Normal Rabbits**

| Rabbit | Normal Hydrochloric Acid, Cc | Blood Sugar, Mg per Hundred Cubic Centimeters of Blood | | | | |
|--------|------------------------------|--|--------|--------|---------|---------|
| | | Control | ½ Hour | 1 Hour | 2 Hours | ¾ Hours |
| 1 | 0.2 | 133 | 200 | 210 | 174 | 140 |
| 2 | 0.2 | 133 | 200 | 185 | 181 | 176 |
| 3 | 0.2 | 117 | 200 | 190 | 170 | 138 |
| 4 | 0.0 | 133 | 200 | 182 | 160 | 151 |
| 7 | 0.0 | 121 | 182 | 157 | 133 | 125 |
| 10 | 0.2 | 115 | 166 | 210 | 140 | 125 |
| 11 | 0.2 | 118 | 180 | 176 | 176 | 140 |
| 12 | 0.2 | 100 | 150 | 130 | 125 | 125 |
| 16 | 0.3 | 110 | 160 | 154 | 131 | |
| 19 | 0.3 | 108 | 163 | 182 | 111 | |
| 19 | 0.3 | 118 | 170 | 133 | 130 | |

* To prevent salivary digestion, 0.2 or 0.3 cc of normal hydrochloric acid was added.

TABLE 2—*The Effect of Ligation of the Pancreatic Duct on the Increase in Blood Sugar after Starch Feeding*

| Rabbit | Day Before or After Operation | Blood Sugar, Mg per Hundred Cubic Centimeters of Blood | | | | |
|--------|-------------------------------|--|--------|--------|---------|---------|
| | | Control | ½ Hour | 1 Hour | 2 Hours | ¾ Hours |
| 1 | Before | 123 | 200 | 210 | 174 | 140 |
| | Second after | 140 | 170 | 146 | 140 | 138 |
| 2 | Before | 133 | 200 | 185 | 181 | 176 |
| | Second after | 116 | 115 | 116 | 118 | 116 |
| | Fifth after | 150 | 160 | 160 | 154 | |
| | Tenth after | 72 | 72 | | 77 | 70 |
| 3 | Before | 117 | 200 | 190 | 170 | 138 |
| | First after | 111 | 111 | | 105 | 102 |
| | Fourth after | 125 | 125 | 133 | 133 | |
| 12 | Before | 100 | 170 | 130 | 125 | 125 |
| | Second after | 120 | 120 | 100 | 116 | 110 |
| | Sixteenth after* | 114 | | 148 | 130 | 121 |
| 16 | Before | 114 | 160 | 154 | 131 | |
| | Third after | 115 | 128 | 131 | 121 | |
| | Fifth after | 111 | 133 | 118 | 118 | |
| | Seventh after | 108 | 128 | 123 | 127 | |
| 19 | Before | 118 | 170 | 123 | 120 | |
| | Before | 108 | 166 | 182 | 118 | |
| | Third after | 90 | 100 | 133 | 105 | |
| | Fifth after | 114 | 153 | 133 | 111 | |
| | Seventh after | 127 | 146 | 133 | 125 | |

* At autopsy the duct was found patent.

In six rabbits fourteen tests were performed from one to ten days after ligation of the pancreatic duct. Either no rise of blood sugar or an increase of 5 to 10 mg per hundred cubic centimeters of blood occurred in four of the rabbits. Rabbit 16 had an average rise of 25 mg per hundred cubic centimeters of blood, and rabbit 20 a rise of 31 mg per hundred cubic centimeters of blood following ligation of the duct. In rabbit 22 a normal curve was obtained on the sixteenth day, at autopsy it was found that the ligature had dis-

appeared from the pancreatic duct, which was not dilated. Methylene blue injected into it entered freely into the intestine. In the other animals, complete obstruction was demonstrated by the injection of dye into the duct. The presence of minute accessory ducts could not be definitely excluded, although a careful search was made for them at autopsy.

APPLICATION AS A METHOD FOR STUDYING UPPER INTESTINAL DIGESTION

The digestion of starch, when salivary action in the mouth and stomach is eliminated, proceeds in the upper intestinal canal. The rate at which this digestion proceeds can be followed fairly closely by a study of the blood sugar. It seemed likely that in normal persons or in persons in whom there is an adequate secretion of pancreatic amylase such a method would be useful for the investigation

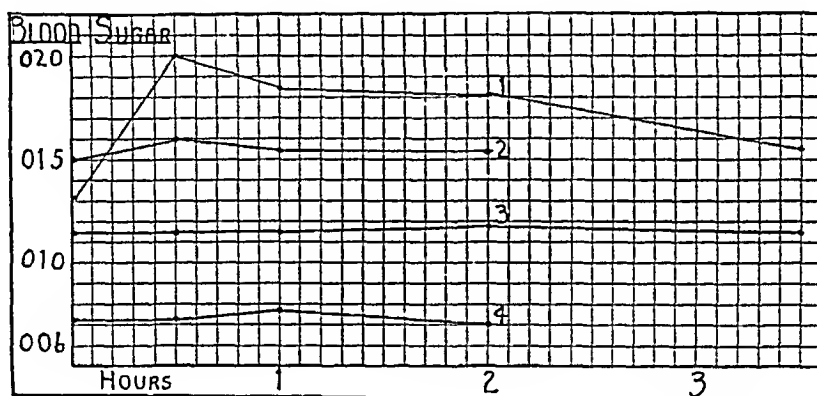


Chart 2—Effect of ligation of pancreatic duct in rabbit 2: curve 1, before operation; curve 2, five days after operation; curve 3, two days after operation; curve 4, ten days after operation.

of various factors or pathologic states which might influence digestion in the upper part of the small intestine.

In view of the high degree of sensitivity of the pancreatic and intestinal enzymes to hydrogen ions, and in view of the fact that in normal persons the reaction of the upper intestinal contents is frequently not the optimum for their action, an attempt was made to study the effect of the administration of increased quantities of acid on the digestion of starch. The acid was added to the starch solution immediately before it was given by stomach tube to the rabbits. Any hydrolysis of the starch which the acid itself might produce would tend to increase the rise in blood sugar. Since a marked depression was always obtained, this source of error can be neglected. Incubation of soluble starch in eight hundredths normal acid at 37° C. for two hours did not produce an appreciable quantity of reducing sugars.

It was a surprise to find that relatively small quantities of acid could appreciably influence the blood sugar changes. The height and shape of the curve were greatly altered when 1 or 2 cc of normal hydrochloric acid (3.65 per cent) was added to the starch solution. The total rise of blood sugar in four rabbits averaged in one half hour 25 mg., in one hour 29 mg., in two hours 21 mg. and in three and one half hours, 13 mg. per hundred cubic centimeters of blood. In six experiments in which 3 or 4 cc of acid was added, the blood sugar increases averaged in one half hour 21 mg., in one hour 18 mg. and in two hours 16 mg. per hundred cubic centimeters of blood. These are striking differences from the averages in eleven experiments, in which from 0.2 to 0.3 cc of acid or none at all was employed. In these the increases of blood sugar averaged at one half hour 62

TABLE 3—*Administration of from One to Four Cubic Centimeters of Normal Hydrochloric Acid with the Starch, Which Markedly Depressed the Rise in Blood Sugar and also Delayed the Return to Normal, Indicating Retardation and Lessened Intensity of Digestion*

| Rabbit | Normal Hydrochloric Acid, Cc | Blood Sugar, Mg per Hundred Cubic Centimeters of Blood | | | | |
|--------|------------------------------|--|--------|--------|---------|----------|
| | | Control | ½ Hour | 1 Hour | 2 Hours | 3½ Hours |
| 5 | 1 | 114 | 133 | 118 | 111 | 141 |
| 6 | 1 | 130 | 160 | 154 | 139 | 130 |
| 6 | 2 | 108 | 125 | 125 | 125 | 117 |
| 8 | 2 | 125 | 162 | 166 | 162 | 110 |
| 7 | 3 | 130 | 142 | 112 | 137 | |
| 4 | 4 | 110 | 125 | 138 | 138 | 138 |
| 7 | 1 | 131 | 154 | 160 | 166 | 166 |
| 7 | 1 | 108 | 154 | 125 | 111 | |
| 15 | 4 | 111 | 122 | 126 | 129 | |
| 20 | 4 | 111 | 130 | 118 | 114 | |

mg., at one hour 54 mg., at two hours 30 mg. and at three and one half hours 16 mg. per hundred cubic centimeters of blood.

The inhibition of digestion from the acid is greatest during the first half hour. It is generally stated that amylase is not only inactivated but rapidly destroyed by acids, but an investigation of this problem with modern methods has not been found. Owing either to the destruction of the enzyme or to the fact that during the time through which these observations were made the reaction of the intestinal contents was never made sufficiently alkaline to approach the p_{H} at which amylase works best (p_{H} 6.8) starch digestion proceeded slowly when acid was given. When more than 2 cc of acid was used as a rule there was no tendency for the blood sugar curve to drop between the first and third hour following starch feeding.

It now remained to prove that the administration of these quantities of acid did not alter the blood sugar changes produced by feeding of starch, either by causing the food to be retained longer in the stomach or by interfering with the intestinal absorption of the products

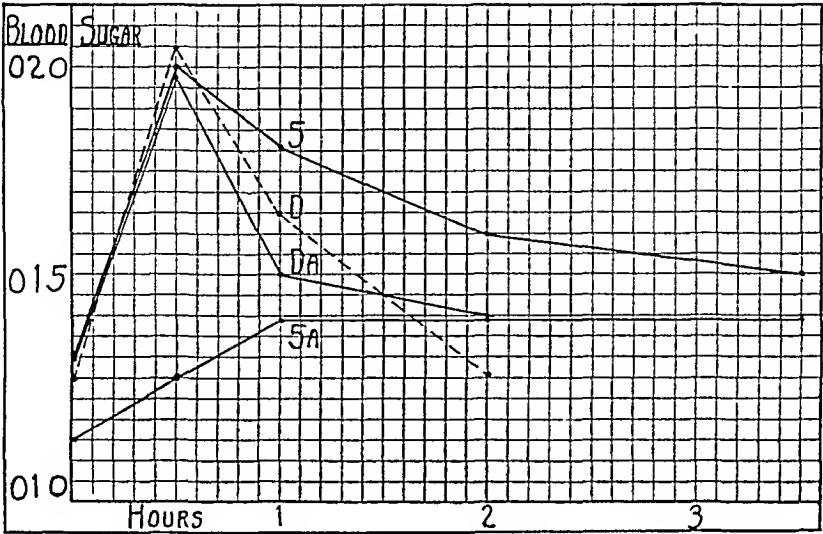


Chart 3—The inhibition of the upper intestinal digestion by acid in rabbit 4 curve 5, blood sugar after the administration of 10 Gm of starch + 0.2 cc of normal hydrochloric acid, curve 5A, after 10 Gm of starch + 4 cc of acid, curve D, after 1 Gm of dextrose (in 60 cc of water), curve DA, after 1 Gm of dextrose + 4 cc of acid

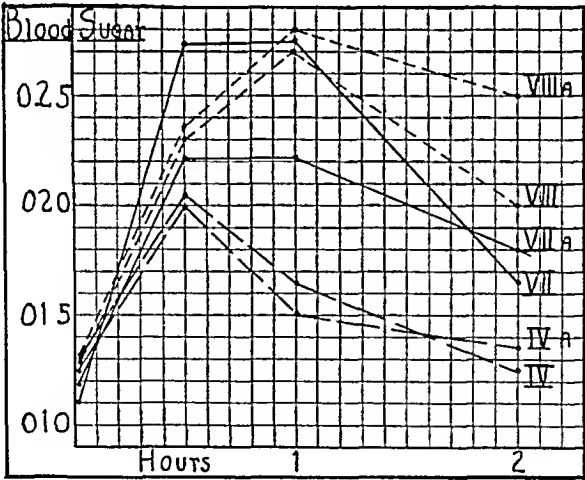


Chart 4—Showing that acid does not appreciably alter the blood sugar curve after the administration of dextrose in rabbit 4, 1 Gm of dextrose with 4 cc of normal hydrochloric acid, (IVa) and without (IV, in rabbit 7, 3 Gm of dextrose + 3 cc of acid (VIIA), in rabbit 8, 5 Gm of dextrose + 4 cc of acid (VIIIa)

of starch digestion This was done by giving to three rabbits 1, 3, and 5 Gm of dextrose in 50 cc of water and determining the blood sugar curves After an interval of several days the tests were repeated, 3 or 4 cc of normal hydrochloric acid being added to the dextrose solutions The shapes of the curves with and without acid were almost identical In rabbit 7 the increase in blood sugar was greater when acid was not given, but in rabbit 8 the reverse tended to hold true These experiments indicate that in the rabbit from 1 to 2 Gm of dextrose will produce a blood sugar curve of a magnitude similar to that obtained from 10 Gm of uncooked starch

COMMENT

There is an apparent field of usefulness for more refined methods of studying the activity of the external pancreatic secretion The promising experimental results obtained with the starch tolerance test justify its application to clinical use and an attempt is at present being made to standardize the procedure for employment in man Preliminary experiments have shown that in man raw starch is digested so slowly that from 50 to 75 Gm do not produce an appreciable rise in blood sugar For this purpose, therefore, cooked starch is being used

The fact that hydrochloric acid so markedly depresses upper intestinal digestion places gastric hypersecretion in a new rôle which may explain some of the digestive and metabolic disturbances seen in this condition For it must be remembered that trypsin, erepsin and lipase are similarly susceptible to hydrogen ions, and that what has been found for carbohydrate digestion probably applies to protein and fat digestion also It is hoped that the carrying out of experiments along similar lines with albumoses and fats will show that this is true

Calculations based on the secretion of hydrochloric acid in the dog⁷ indicate that the rabbit would produce in the neighborhood of from 1 to 4 cc of normal hydrochloric acid during a meal A part of this would be combined with the food proteins but the amounts used do not vary far from physiologic limits

The bile is an important factor in the neutralization of the acid gastric contents, and intestinal digestion in obstructive jaundice deserves study from this method of approach

CONCLUSIONS

In a series of ten rabbits, 10 Gm of uncooked starch in slightly acid solution was administered by stomach tube A uniform rise in blood sugar resulted, averaging 62 mg per hundred cubic centimeters of blood

⁷ Rosemann, R Arch f Physiol 118 467, 1907

Tests repeated after ligation of the pancreatic duct showed either no rise in blood sugar or an increase of from 5 to 31 mg per hundred cubic centimeters of blood

The addition of from 1 to 4 cc of normal hydrochloric acid to the starch markedly altered the height to which the blood sugar rose in normal rabbits. The shape of the blood sugar curve was also changed, indicating that starch digestion was greatly inhibited during the first hour following its administration, and then proceeded at a slow rate over a period that was much more prolonged than normal. That this was due to the depressing effect of the acid on the activity of the intestinal enzymes was shown by the fact that similar quantities of acid added to solutions of dextrose did not appreciably alter the tolerance for dextrose.

THE ANTAGONISM BETWEEN INSULIN AND PITUITARY EXTRACT

ITS DEMONSTRATION IN A PATIENT WITH ACROMEGALY *

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The pituitary body has for a long time been known to play a part in the mechanism that controls carbohydrate metabolism. Goetsch, Cushing and Jacobson¹ noted the high carbohydrate tolerance that accompanies pituitary deficiency, and they confirmed Borchardt's² previous assertion that the injection of pituitary extract caused hyperglycemia.

Stenstrom³ made the apparently conflicting observation that pituitary extract inhibited the hyperglycemia and glycosuria caused by injections of epinephrine hydrochloride. This was afterward confirmed by Burn⁴ who was led thereby to speculate that pituitary extract should enhance the action of insulin. He found the opposite to be true,⁵ namely, that posterior lobe extract, when injected into rabbits simultaneously with insulin, "had a powerful antagonistic effect on the action of insulin" as well as on that of epinephrine hydrochloride.

Olmstead and Logan⁶ in their work with decerebrated cats, reached the same conclusion, and the studies of Joachimoglu and Metz,⁷ Laura⁸ and others added further confirmation.

* From the Evans Memorial for Clinical Research and Preventive Medicine.

1 Goetsch, E, Cushing, H, and Jacobson, C. Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, *Bull Johns Hopkins Hosp* **22** 165, 1911.

2 Borchardt, L. Experimentelles über den Diabetes bei der Akromegalie, *Deutsche med Wchnschr* **34** 946, 1908.

3 Stenstrom, T. Das Pituitrin und die Adrenalinhyperglykämie, *Biochem Ztschr* **58** 472-482, 1913.

4 Burn, J H. Hyperglycemia Produced by Adrenalin and by Anesthesia, *J Physiol, Proc Physiol Soc*, Jan 23, 1915, vol 49.

5 Burn, J H. The Modification of the Action of Insulin by Pituitary Extract and Other Substances, *J Physiol* **57** 318, 1923.

6 Olmstead, J M D, and Logan, H D. The Effect of Insulin on the Central Nervous System and Its Relation to the Pituitary Body, *Am J Physiol* **66** 437 (Oct) 1923.

7 Joachimoglu, G, and Metz, A. Ueber den Antagonismus von Insulin und Hypophysenpräparaten, *Deutsche med Wchnschr* **50** 1787 (Dec 19) 1924.

8 Laura, L. Stato presente della teoria pancreatica del diabete e della relazione tra insulina e pituitrina, *Riforma med* **41** 582 (June 22) 1925.

Moehlig and Ainslee⁹ believed that the antagonism of pituitary extract consisted of a conversion of muscle glycogen to dextrose. Lawrence and Hewlett¹⁰ were of the same opinion. They found, furthermore, that the usual small dose of pituitary extract (1 cc) inhibited the hypoglycemic effects of insulin given at the same time.

In a different sphere of action, Serebrijski and Vollmer¹¹ and Koref and Mautner¹² proved that both insulin and pituitary extract, when used separately, reduced the excretion of water by the kidneys, but that this inhibitory action was nullified when they were given together. Then water excretion occurred in a normal manner. And Coope¹³ who, with Chamberlain,¹⁴ had previously shown that injections of pituitary extract caused fatty infiltration of the liver of rabbits, discovered that the simultaneous injection of insulin profoundly modified and often prevented this effect. This suggests that the antagonism between these hormones is not one-sided, that is, of pituitary extract against insulin only, but reciprocal.

All of the quoted experimental research indicates that loss of carbohydrate tolerance in hyperpituitary disease is due to an antagonistic inhibitory action exercised by excessive pituitary secretion, probably of the posterior lobe, on normal insulin function. If this assumption is correct, then the use of insulin in the treatment of patients with hyperpituitary glycosuria should prove partially or wholly ineffective.

Falta¹⁵ reported the case of an insulin refractive patient with glycosuria, whose low basal metabolic rate, obesity and extremely small sella suggested to him a hypophysial influence. In the case of Mahler and Pasterny¹⁶ the patient had a proved pituitary tumor. Sixty units of insulin did not affect the hyperglycemia.

9 Moehlig, R. C., and Ainslee, H. B. Antagonistic Action of Posterior Pituitary Extract and Insulin, *J. A. M. A.* **84** 1398 (May 9) 1925.

10 Lawrence, R. D., and Hewlett, R. F. L. The Effect of Pituitrin and Insulin on Blood Sugar, *Brit. M. J.* **1** 998 (May 30) 1925.

11 Serebrijski, F., and Vollmer, H. Zum Antagonismus zwischen Insulin und Hypophysenhormon, *Klin. Wchnschr.* **4** 2256 (Nov. 19) 1925.

12 Koref, O., and Mautner, H. Ueber den Einfluss von Pituitrin und Insulin auf den Wasserhaushalt, *Monatschr. f. Kinderh.* **31** 303, 1925.

13 Coope, R. Insulin and Pituitrin "Fat Liver," *J. Physiol.* **60** 92 (May) 1925.

14 Coope, R., and Chamberlain, E. N. The Effect of Pituitrin on the Fatty Acid of the Liver, *J. Physiol.* **60** 69, 1925.

15 Falta, W. Ueber einen insulinrefraktaren Fall von Diabetes mellitus, *Klin. Wchnschr.* **3** 1315 (July) 1924.

16 Mahler, P., and Pasterny, K. Klinische Beobachtungen uber Insulinwirkung beim Diabetes mellitus, *Med. Klin.* **20** 337 (May 16) 1924.

Cushing,¹⁷ John¹⁸ and Hetzel,¹⁹ however, stated, in effect, that pituitary diabetes does not differ from pancreatic diabetes in its response to insulin therapy. Cushing has apparently come to a different conclusion, because in a recent paper of his, written jointly with Davidoff,²⁰ the belief is expressed that insulin may be less effective in patients with pituitary glycosuria than in those with pancreatic diabetes. John's two case reports, one of which will be discussed later, are not convincing and lend themselves readily to an entirely different interpretation. Hetzel's case, too, will be taken up again, and, according to Hetzel's own words, the patient will be shown to have been refractory to insulin, despite the conclusion that insulin treatment was effective.

The following study of a patient with acromegaly and hyperglycemia is presented in support of the quoted laboratory evidence that antagonism between pituitary extract and insulin exists and may be clinically demonstrable.

REPORT OF CASE

L. D. C., a man, aged 24, was admitted to the Evans Memorial Hospital on July 3, 1924, for endocrine study. A diagnosis of pituitary neoplasm was made, based on the presence of headache, characteristic changes in the ocular fundi and color fields, a basal metabolic rate of minus 11 and an enlarged sella turcica with a shallow and eroded floor. At this time glycosuria was not found. He was discharged in two weeks and readmitted a month and a half later, complaining particularly of headache. Glycosuria was absent.

The patient's next entry was on Dec. 13, 1924, when he complained of marked thirst, polyuria and weakness. Glycosuria was now present, the sugar in the urine amounting to 238 Gm. in twenty-four hours.

In view of Cushing's¹⁷ statement that "we know that acromegalic glycosuria is associated with a hyperglycemia, and that it reacts to insulin as does pancreatic diabetes," difficulty was not expected in the attempt to control glycosuria in this patient.

He was given 10 units of insulin before each meal and a diet containing approximately 80 Gm. of protein, 160 Gm. of fat and 60 Gm. of carbohydrate (chart 1). The blood sugar was 404 mg. per hundred cubic centimeters of blood. After two days of insulin treatment, the urine sugar was 81.8 Gm. This was a satisfactory reduction, but, to hasten results, the amount of insulin was doubled. The blood sugar did not decrease but increased to 500 mg. The dosage of insulin was increased to 40 units three times a day, but the blood sugar increased further to 625 mg. This led to another doubling of insulin dosage to 80 units before each meal. Glycosuria decreased, the sugar in the urine amounting to 40 Gm., and the blood sugar to 285 mg.; nevertheless, the dosage of insulin was increased to the huge amount of 120 units three times a day. Glycosuria

¹⁷ Cushing, H. The Pituitary Gland as Now Known, *Lancet* **2** 899 (Oct. 31) 1925.

¹⁸ John, H. J. The Possible Relationship Between Acromegaly and Diabetes, *Arch. Int. Med.* **37** 489 (April 15) 1926.

¹⁹ Hetzel, K. S. Glycosuria in Acromegaly, *Lancet* **1** 440 (Feb. 27) 1926.

²⁰ Davidoff, L. M., and Cushing, H. Studies in Acromegaly. VI. The Disturbances of Carbohydrate Metabolism, *Arch. Int. Med.* **39** 751 (June) 1927.

unaffected Insulin was then discontinued, and dietetic restrictions were removed The blood sugar promptly increased to 500 mg These effects and others caused by changes of diet and variations in the dosage of insulin are depicted on chart 2, which covers the period of his stay in the hospital

Analysis of charts 1 and 2 must lead to the conclusion that insulin had but little effect on the blood sugar level of this patient during the periods covered by these charts (The postoperative hyperglycemia, which may have been due to surgical trauma, appeared to be more responsive) One should note, particularly, in the first half of chart 1, the increasing blood sugar while insulin was being increased and, in the second half of this chart, the persistent decline of hyperglycemia, despite a fairly rapid decrease in the dosage of insulin from the huge total of 360 units a day to nothing At first glance it may appear that

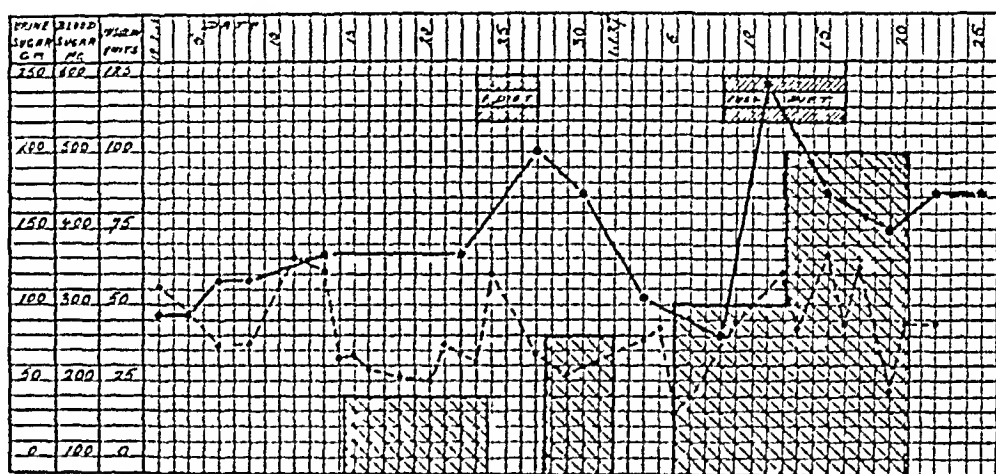


Chart 2—Blood sugar variations are indicated by the solid line, glycosuria by the broken line The dosage of insulin is shown by the large hatched blocks A diabetic diet was given throughout, except as indicated

insulin treatment was responsible for this lowering of the blood sugar level Closer study of the chart disproves this It should be noted especially that without insulin, even with unrestricted diet, the blood sugar remained normal

It is known that glycosuria accompanying hyperpituitary disease may disappear spontaneously, regardless of treatment John²¹ and Hetzel¹⁹ reported cases of acromegaly, previously cited, in which this occurred Indeed, their cases seem to be similar to the one reported here But John believed that the elimination of glycosuria in his patient was due to dictetic restrictions and the use of insulin and that the case was one of cured pancreatic diabetes Hetzel came to the conclusion that in his patient "The glycosuria was identical with that of diabetes, it

21 John, H J Spontaneous Disappearance of Diabetes, J A M A 85 1629 (Nov 21) 1925

reacted similarly to insulin and control of the diet" This conclusion, however, does not agree with the text of his case report There he stated that "the efficacy of insulin was doubtful" and that it "had only a small effect on the blood sugar"

To be sure, in his case as in John's, all evidences of diabetes finally vanished, and it may have been this fact that brought Hetzel to the foregoing conclusion But insulin does not act in that way Its intensive use, as has been shown,²² may raise the carbohydrate tolerance of children and young adults a little, but it does not cure diabetes Both Hetzel and John were apparently misled, in that they misinterpreted a spontaneous recession of pituitary hyperglycemia as an effect produced by insulin

Sachs and MacDonald²³ reported the case of a woman who was operated on for "acute acromegaly" The operation was followed by glycosuria which, they stated, "in no way differed from glycosuria of a diabetic patient," and which "was furthermore controlled by administration of insulin" Glycosuria was apparently not present before operation, so that in this patient it must be regarded as a result of operative trauma rather than as a symptom of pituitary disease This places the case in an entirely different category and does not prove the efficacy of insulin in true hyperpituitary glycosuria

The only seemingly valid evidence of efficient insulin action in this type of glycosuria is furnished by Blum and Schwab²⁴ They gave 30 units of insulin to each of two patients, one suffering from acromegalic glycosuria, and the other from pancreatic diabetes The responses were essentially equal

This may mean that there are gradations of antagonism in different patients with hyperpituitary disease, ranging in intensity from none at all, as in the case of Blum and Schwab, to almost complete inhibition, as in my case Or, if it is true that pituitary tumors may give rise to glycosuria by pressure on neighboring brain centers the simultaneous presence of this pressure type, which may be amenable to insulin, with a hypersecretory type, would lead to varying degrees of responsiveness to treatment with insulin Again, it is conceivable that some of the patients may develop true pancreatic diabetes, owing to exhaustion of the pancreas from constant stimulation by the pituitary

22 Ulrich, H Induced Hypoglycemia as a Means of Resting and Improving Pancreatic Function in Patients With Diabetes, *J A M A* **83** 1914 (Dec 13) 1924

23 Sachs, E, and MacDonald, M E Blood Sugar Studies in Experimental Pituitary and Hypothalamic Lesions, *Arch Neurol & Psychiat* **13** 335 (March) 1925

24 Blum, L, and Schwab, H Diabete acromegalique et insuline, *Compt rend Soc de biol* **89** 195 (June 8) 1923

hyperglycemia Such patients may then become more susceptible to treatment with insulin

Chart 2 shows clearly that the hyperglycemia of my patient was influenced markedly by dietetic changes, and the second half of this chart suggests that insulin also had a slight effect To ascertain more definitely the direct action of insulin, uncomplicated by dietetic influence, large doses were given before breakfast on four widely separated days as illustrated on chart 3 On each of three of these occasions the amount of insulin was 50 units, and on one it was 100 units Blood sugar determinations were made at varying intervals after the injections of insulin Food was not allowed until after the last specimen of blood of that day had been drawn Similar tests to serve as controls were conducted with four patients suffering from so-called pan-

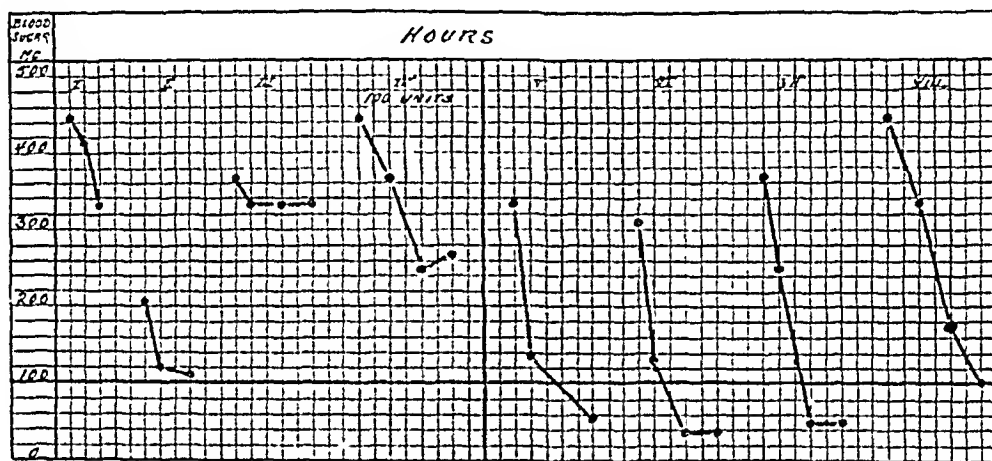


Chart 3—Changes in the blood sugar level following injections of insulin with the patients in the fasting state The amount of insulin given was 50 units in each instance, except in experiment IV, when 100 units was used Curves I to IV represent the blood sugar responses of the patient with acromegaly Curves V to VIII show the responses of four patients with pancreatic diabetes The first blood sugar value in each case was obtained immediately before the injection of insulin, the others, as shown on the chart, at varying intervals afterward

creatic diabetes The curves depicting these tests are plotted at the right of chart 3

In the patient with acromegaly, the injection of insulin was followed in at least three of the four tests by a definite lowering of the blood sugar level If curve I had been extended, it might possibly have shown a further depression of glycemia Aside from this possibility, however, a comparison of the two sets of curves shows decidedly different results The extent of the reduction of blood sugar was much greater in the patients with pancreatic diabetes Three of them became markedly hypoglycemic and developed symptoms of severe insulin shock

Comparison of curves IV and VIII is particularly instructive. Both show blood sugar values of 444 mg before the injection of insulin. The patient with acromegaly received 100 units and responded with a decrease to 250 mg, the patient with diabetes received only 50 units, but the decrease in his blood sugar was more than twice as great.

SUMMARY

1 Medical literature contains much experimental evidence that the internal secretion of the posterior pituitary lobe antagonizes insulin.

2 A case of hyperpituitary disease with acromegaly and glycosuria is reported, in which this antagonistic action is demonstrated.

3 The opinion is expressed that this antagonism may vary in different patients.

4 Insulin may, therefore, show varying degrees of efficiency in the treatment of hyperpituitary loss of carbohydrate tolerance.

5 In the case reported, its effectiveness was much impaired.

ACROMEGALY AND DIABETES

REPORT OF SIX CASES *

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It is assumed in this paper that acromegaly is a constitutional disease of adult life due to overactivity of the anterior lobe of the pituitary gland, manifest pathologically by a hyperplastic or adenomatous process composed of acidophilic cells¹. Since the first comment on the frequent occurrence of mellituria in persons with tumor of the hypophysis, made by Loeb² in 1884, there has been much experimentation and much discussion concerning the relationship of the pituitary gland to the diabetes. The hypotheses thus far advanced are

- 1 In the hypothalamus in the neighborhood of the hypophysis, there is a center which regulates carbohydrate metabolism. In acromegaly, the pressure of a large tumor of the pituitary gland on this center causes the diabetes.

- 2 The glycosuria is due to secondary changes in the pancreas.

- 3 There is a disturbance of the internal secretion of the thyroid gland, which impairs the functional ability of the islands of Langerhans.

- 4 An excess of secretion of the posterior lobe of the pituitary gland itself is responsible for the diabetes, probably by stimulating glycogenolysis in the glycogen reservoirs and thus supplying glucose at a rate beyond the ability of the tissues to utilize it.

- 5 The hypophysis itself contains nerve centers or tracts which are effective in producing such an excessive glycogenolysis.

- 6 The hypophyseal secretion or a nerve center in or near the hypophysis serves to check the rate of secretion of insulin from the islands of Langerhans.

* Work done in the Division of Medicine, Mayo Clinic, under the direction of Russell M. Wilder.

1 Bailey, Percival, and Davidoff, L. M. Concerning the Microscopic Structure of the Hypophysis Cerebri in Acromegaly. *Am. J. Path.* **1**: 185, 1925.
Cushing, Harvey, and Davidoff, L. M. Studies in Acromegaly. V. The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of their Significance, Monograph, New York, Rockefeller Inst. Med. Res., 1927, vol. 22.

2 Loeb, M. Ein Erklärungsversuch der verschiedenartigen Temperaturverhältnisse bei der tuberculösen Basilarmeningitis, *Deutsches Arch. f. klin. Med.* **34**: 443, 1884.

7 The internal secretion of the pituitary gland is directly antagonistic to insulin and nullifies its effect

The results of experimental and clinical investigations regarding the relationship of the pituitary gland to carbohydrate metabolism may be summarized as follows

1 Acromegaly is found to be complicated by diabetes mellitus more frequently than by any other disease. It has been estimated in various series of cases of acromegaly that diabetes occurs in from 9 to 40 per cent, with an average, probably, of from 10 to 12 per cent. These figures are subject to two errors. In many cases, the diagnosis of diabetes rests on insufficient data, such as the presence of glycosuria alone, in other cases, the patients were not examined sufficiently often or followed long enough to justify any conclusions as to whether diabetes had been present or would develop. Nevertheless, the frequency is so striking as to suggest more than an accidental relationship. Borchardt,³ tabulating the cases from the literature up to 1908, found that there were 63 (35.5 per cent) which were complicated by frank diabetes and 8 more which were associated with at least an alimentary glycosuria. Davidoff⁴ reported that in 25 of Cushing's 100 cases of acromegaly mellituria was evident and that in 12 of these frank diabetes was present.

2 Glycosuria and diabetes are uncommon in nonacromegalic disorders of the hypophysis, such as tumors of the hypophysis itself not accompanied by acromegaly and lesions in the vicinity of the hypophysis which cause pressure on the gland or invade it secondarily. Colwell,⁵ however, found, even after an incomplete survey, 38 cases of nonacromegalic disorders of or near the hypophysis accompanied by glycosuria or diabetes, and suggested that this number compares favorably with the incidence of glycosuria or diabetes in patients with acromegaly.

3 Hypopituitarism is rarely associated with glycosuria, increased tolerance is a usual occurrence. The syndrome of obesity, delayed development of the sexual organs and functions, lack of secondary sex characteristics and inferior mental capacity, has been assigned to a deficiency of pituitary secretion because of the demonstration in such cases of destructive lesions involving the hypophysis and because of the experimental production of such a syndrome by extirpation of

3 Borchardt, L. Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, *Ztschr f klin Med* **66** 332, 1908.

4 Davidoff, L. M. Studies in Acromegaly. III. The Anamnesis and Symptomatology in One Hundred Cases, *Endocrinology* **10** 461, 1926.

5 Colwell, A. R. The Relation of the Hypophysis to Diabetes Mellitus, *Medicine* **6** 1, 1927.

the hypophysis in animals Goetsch, Cushing and Jacobson,⁶ especially, have been responsible for this view and have demonstrated the increased tolerance for carbohydrates in such cases. These investigations also showed that hyperglycemia induced by removal of a large portion of the pancreas tended to subside when partial hypophysectomy was later performed, and, conversely, that when animals had acquired a high sugar tolerance with hypoglycemia after hypophysectomy, they bore the removal of a large portion of the pancreas with less disturbance of carbohydrate balance than the normal animal would. This work and that of others has been criticized, however, because the alimentary glucose tolerance test was used. Moreover, Gibson⁷ reported a typical example of hypopituitarism in which diabetes existed, and John⁸ reported 5 cases of clinical hypopituitarism with glycosuria or decreased sugar tolerance (oral method of administration), which represented 12 per cent of the cases of hypopituitarism at the Cleveland Clinic. However, in the entire series of 185 cases from the Peter Bent Brigham Hospital in which the diagnosis of pituitary tumor recorded as "chromophobe" was verified histologically, only 4 were proved to have been associated with even transient glycosuria. Wilder and Sansum,⁹ giving glucose intravenously continuously and at a constant rate in 2 patients with Frolich's syndrome, observed essentially the same limit of assimilation as in 4 normal controls. They concluded that the increased tolerance demonstrated by those who used the oral method might have been due to some such factor as delayed absorption.

4 Transient glycosuria follows removal of the hypophysis in animals (first shown by Caselli,¹⁰ in 1900 and by Friedman and Maas¹¹ in the same year and confirmed by many other investigators). Goetsch, Cushing and Jacobson⁶ found that any operative manipulation of the gland would frequently cause glycosuria. Weed, Cushing and Jacobson¹² observed that direct mechanical or electrical manipulation of the

6 Goetsch, Emil, Cushing, Harvey, and Jacobson, Conrad. Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, *Bull. Johns Hopkins Hosp.* **22** 165, 1911.

7 Gibson, H. J. C. Hypopituitarism Associated with Glycosuria, *Edinburgh M. J.* **31** 82, 1924.

8 John, H. J. Spontaneous Disappearance of Diabetes, *J. A. M. A.* **85** 1629 (Nov. 21) 1925, The Possible Relationship between Acromegaly and Diabetes, *Arch. Int. Med.* **37** 489 (April) 1926.

9 Wilder, R. M., and Sansum, W. D. d-Glucose Tolerance in Health and Disease, *Arch. Int. Med.* **19** 311 (Feb.) 1917.

10 Caselli, A., quoted by Colwell (footnote 5).

11 Friedman, F. F. and Maas, Otto. Ueber Extirpation der Hypophysis cerebri, *Berl. klin. Wchnschr.* **37** 1213, 1900.

12 Weed, L. H., Cushing, Harvey, and Jacobson, Conrad. Further Studies on the Role of the Hypophysis in the Metabolism of the Carbohydrates, *Bull. Johns Hopkins Hosp.* **24** 40, 1913.

hypophysis of rabbits, cats and dogs under ether anesthesia invariably produced glycosuria (provided the liver contained sufficient glycogen) They demonstrated, also, that glycosuria followed mechanical or faradic stimulation of the superior cervical sympathetic ganglions and did so even after all of the known nerve paths to the viscera had been severed They observed that glycosuria did not take place following stimulation of the superior cervical ganglion when the posterior lobe of the hypophysis had previously been removed They thought that these results showed that the secretion of the posterior lobe itself and not direct stimulation of the liver by a nerve route was responsible for the glycosuria The work, however, has never been confirmed

5 In 1909, Aschner¹³ provoked glycosuria in an animal for two days by injury to the hypothalamic region in the floor of the third ventricle In 1912,¹⁴ he reported studies showing that glycosuria was almost always caused by injury of the tuber cinereum This result was confirmed by others Camus, Gounay and Le Grand¹⁵ were able to produce prolonged glycosuria by injury of this organ, and in one animal it lasted forty-seven days Sachs and MacDonald¹⁶ showed that when the base of the brain was not injured during hypophysectomy, glycosuria did not occur, but that it did so only when the brain region of the floor of the third ventricle was injured whether the hypophysis was removed or not

6 Injection of pituitary extracts often produces transitory glycosuria and hyperglycemia This has been demonstrated by many investigators, but a few have failed to confirm it

7 Goetsch, Cushing and Jacobson⁶ observed that the high sugar tolerance of some of their animals (alimentary test), even when accompanied by hypoglycemia, could be overcome and glycosuria provoked by the hypodermic injection of anterior lobe as well as posterior lobe extracts Houssay and Magenta¹⁷ reported that dogs, after the establishment of hypopituitarism by hypophysectomy, were more easily rendered hypoglycemic by the injection of insulin than normal dogs

13 Aschner, Bernhard Ueber das "Stoffwechsel- und Eingeweidezentrum im Zwischenhirn" seine Beziehung zur inneren Sekretion (Hypophyse, Zirbeldrüse) und zum Diabetes insipidus, *Berl klin Wchnschr* **2** 772, 1916

14 Aschner, Bernhard Ueber die Funktion der Hypophyse, *Arch f d ges Physiol* **146** 1, 1912

15 Camus, J, Gournay, J J, and LeGrand, A Diabete sucre experimental, *Comp rend Acad d sc* **177** 146, 1923

16 Sachs, Ernest, and MacDonald, M E Blood Sugar Studies in Experimental Pituitary and Hypothalamic Lesions with a Review of Literature, *Arch Neurol & Psychiat* **13** 335 (March) 1925

17 Houssay, B A, and Magenta, M A Sensibilite des chiens hypophysectomises a laigaid de l'insuline, *Comp rend Soc de Biol* **92** 822, 1925

All of the hypophysectomized dogs had convulsions and died, whereas the control animals did not have convulsions and survived. Other investigators, however, have demonstrated the same increased sensitivity to insulin following injury of the infundibulum alone. Olmstead and Logan¹⁸ were unable to produce any substantial reduction of blood sugar by the injection of insulin in decerebrate cats only when the hypophysis was left intact, but demonstrated severe insulin reactions with hypoglycemia and convulsions when the hypophysis was removed with the cerebrum.

8 Burn¹⁹ demonstrated in animals that pituitary extract is capable of preventing and relieving hypoglycemia and convulsions produced by the injection of insulin. Three of Davidoff and Cushing's²⁰ patients, who had been shown to respond normally to insulin, did not respond as expected (insufficient fall in blood sugar concentration) when 20 units of insulin were combined with 1 cc of pituitary.

9 Stenstrom²¹ found that pituitary inhibited the hyperglycemia due to the administration of epinephrine, and Aschner²² observed that the glycosuric effect of epinephrine in hypophysectomized dogs was less constant than in normal animals.

10 The results of hypophysectomy in man have not satisfactorily demonstrated amelioration of the diabetes. It is true, however, that it is extremely difficult to remove all of the gland, and also that the patients have not been sufficiently carefully observed after operation in the majority of cases. Davidoff and Cushing²⁰ reported only one instance from 14 cases of acromegaly and diabetes in which there was immediate cessation of the glycosuria after operation for pituitary adenoma. Three days after operation the blood sugar content was 0.12 per cent, and glycosuria was not present during the following month up to the time of dismissal. In view of the fact that the pre-existing diabetes had been mild and only recently discovered and that while in the hospital the patient may not have been consuming as much carbohydrate food as previously, this case is not satisfactory proof of any causal relationship of the pituitary condition to the diabetes. Ellis²² reported a case in which he claimed that the diabetes

18 Olmsted, J. M. D., and Logan, H. D. The Effect of Insulin on the Central Nervous System and its Relation to the Pituitary Body, *Am J Physiol* **66** 437, 1923.

19 Burn, J. H. The Modification of the Action of Insulin by Pituitary Extract and other Substances. *J Physiol* **57** 318, 1923.

20 Davidoff, L. M., and Cushing, Harvey. Studies in Acromegaly. VI. The Disturbances of Carbohydrate Metabolism, *Arch Int Med* **39** 751 (June) 1927.

21 Stenstrom, Thor. Das Pituitrin und die Adrenalinhyperglykämie, *Biochem Ztschr* **58** 472, 1914.

22 Ellis, A. W. M. Hyperglycaemia and Glycosuria in Acromegaly with Pathological Report by Prof. H. M. Trumbull, *Lancet* **1** 1200, 1924.

was relieved following hypophysectomy, but three years after the radical extirpation of a pituitary adenoma, the fasting blood sugar content was 0.18 per cent and the glucose tolerance test gave a definitely diabetic curve although the diabetes for some time following the operation was less intense. The patient, however, had been on a diabetic regimen.

Davidoff and Cushing²⁰ tested the glucose tolerance in 9 patients with acromegaly, using the intravenous method, before and after hypophysectomy, in 4, a distinct improvement in tolerance was evidenced by a decrease in the blood sugar level. In all but 1 of these 4 cases, there had not been any clinical evidence of diabetes before operation, in 1, mild clinical diabetes was present. In the case in which greatest improvement in tolerance was manifested, the operation was the most radical, in those in which improvement was the least marked the least tissue was removed. Davidoff and Cushing also called attention to the fact that these patients before operation and a few others who were not operated on gave tolerance curves in which the blood sugar rose to a higher level than the normal and, with a single exception, remained higher than the normal throughout the period of examination. One of John's⁸ patients, also, did not show glycosuria but "there was a slight leaning toward impairment of carbohydrate function," as shown by a glucose tolerance test.

11 The diabetes occurring in persons with acromegaly is in all essential respects similar to the diabetes in the absence of acromegaly. John⁸ stressed this point with 2 case reports, and Colwell² reported a carefully studied case in which this statement was substantiated. In most cases polydipsia and polyuria have been proportionate to the severity of the diabetes. These symptoms and the glycosuria respond to dietetic management as in ordinary diabetes. The glycosuria may be intermittent and detectable only after excessive ingestion of carbohydrate. The diabetes is often relatively mild but some patients have succumbed to diabetic coma. It has often been stated that the diabetes complicating acromegaly runs an irregular course. Colwell studied the literature carefully with this point in mind and collected reports of 17 cases in which an atypical course was claimed to occur. He concluded that in some of these, dietetic control had not been established. In others there appeared to have been a bona fide improvement in the diabetes, and in a few an apparently spontaneous disappearance of the diabetes. Cushing⁶ has been an ardent advocate of the theory "that in the early stages of acromegaly the sugar tolerance test is apt to be low but that later in the disease there is an acquired overtolerance," this is a clinical observation based mainly on the results of tolerance tests for sugar as estimated by the amount necessary to produce glycosuria when taken by mouth. The diabetes associated with acromegaly

responds to insulin as it does in the ordinary form. Several of the cases in the present series demonstrate this point clearly, the subject will be discussed further.

In a series of 79 patients with acromegaly examined at the Mayo Clinic, glycosuria has been observed in 8. Many of the 79 patients were examined on only one occasion. Six of those who manifested glycosuria were studied from the standpoint of the diabetes sufficiently to establish the diagnosis of true diabetes mellitus. Of the other 2 cases, glycosuria was present in one to the extent of 0.8 per cent on one urinalysis only, in the second, 800 cc of urine contained 11.36 Gm of glucose (1.37 per cent) and the blood sugar was 180 mg per cent, but there was no sugar in the urine in a test made one week later. The 6 cases that were more carefully studied are reported in this paper. The authenticity of the acromegaly in one of these (case 4) may be questioned. The history of enlargement of the acral parts and features was lacking and signs of pressure were not present. However, the appearance of the patient was so striking as to suggest acromegaly at once to all the clinicians who saw her. The enlargement of the sella turcica roentgenoscopically further strengthened the impression. The pathologist could not state definitely that the condition was or was not acromegaly, but he admitted that the pituitary gland was larger than normal and showed signs of increased activity as well as several small chromophilic adenomas and an occasional mitotic figure. Insulin was employed in the treatment of 3 of the 6 patients, and, because of the scarcity of reports of cases in which the effects of insulin on the diabetes have been observed, two of these are recorded in some detail.

Two other cases in which frank diabetes was not evident deserve brief mention. In one a hyperfunctioning adenomatous thyroid was present, and the oral administration of 100 Gm of glucose was followed by a diabetic blood sugar curve, thyroidectomy was performed, but a further study of the blood sugar was not made. In the other, a case complicated by exophthalmic goiter, glycosuria was discovered during preparation for thyroidectomy, 55 units of insulin was given daily, although the only estimations of blood sugar before that time revealed a level of 83 and 125 mg per cent. The insulin was continued for four days after thyroidectomy, glycosuria was not evident thereafter.

REPORT OF CASES

CASE 1—Acromegaly of more than fifteen years' duration with greatly enlarged sella turcica, but without signs of pressure, diabetes mellitus of ten years' duration, easily controlled by diet alone.

On June 13, 1925, a laborer, aged 49, appeared for examination at the Mayo Clinic with the complaints of diabetes, headaches and impaired vision. The

family history was irrelevant. He was a widower with two children living and well. He had had diphtheria at the age of 6 and influenza in 1918, at one time a nasal operation had been performed, the details of which were not obtainable. Acromegaly had been diagnosed fifteen years before and he had noticed enlargement of the hands a year prior to that. The acromegaly had gradually progressed since that time. He had suffered from dull bilateral and supra-orbital headaches for twenty years, but these were not as severe as formerly. He had been well otherwise until ten years before admission when he began to drink about a gallon and a half of water daily; the polydipsia was accompanied by polyuria and polyphagia. Glycosuria had not been discovered until five years later and since then thirst or polyuria had not been present when the patient was on a qualitative restriction of carbohydrates. Glycosuria had been present during the last five years whenever the urine had been examined. There had not been any loss of weight. For the last fourteen months, the patient had not been careful in the matter of diet but had taken from 5 to 15 units of insulin "double strength" each morning. There had been some blurring of vision for the last ten years and loss of sexual desire for the same length of time. General weakness had prevented the patient from working during the last five years. He had complained of dizziness for two or three years, numbness of both legs from the knees down for two years and a running sore on the right great toe for one year.

The patient was large, being 6 feet 2 inches (188 cm) tall and weighing 242 pounds (110 Kg). There was general overgrowth of the skeleton, including especially the frontal eminences, the zygomatic processes, malar and nasal bones, the lower jaw and the hands and feet. The teeth were separated. The skin and subcutaneous tissues were thickened, and the skin was dry and scaly. The eyelids were thickened. There were multiple pigmented nevi scattered over the body, especially on the back. There was a foul smelling "trophic" ulcer over the outer surface of the first right metatarsophalangeal joint. The teeth were in bad condition. The tonsils were enlarged and contained liquid pus. The thyroid gland was small, but was palpable, firm and slightly nodular. The heart was moderately enlarged to the left, with a soft systolic murmur at the apex and an occasional premature contraction. The blood pressure was 130 systolic and 74 diastolic, the pulse rate was 74 and the temperature, 98.4 F. The abdomen was pendulous and the liver moderately enlarged. The gait was moderately ataxic. The right adductor pollicis and hypothenar eminence were atrophied. There was some diminution of sensation below the knees. The reflexes were present but sluggish. Both great toes showed a tendency to go into plantar extension. Vision in the right eye was 6/10 and in the left 6/5. The light reflex was somewhat cut down in both eyes. There was moderate retinitis of mixed diabetic and vascular types. The visual fields were normal.

Urinalysis showed a specific gravity of 1.041, acid reaction, no albumin, 2.4 per cent sugar, with 27.5 Gm. in 1,100 cc (twelve-hour specimen), no acetone or diacetic acid, and negative microscopic examination. The hemoglobin was 75 per cent, the erythrocytes numbered 4,530,000 and the leukocytes 6,600. The blood urea was 30 mg per cent and the blood sugar, 300 mg per cent. The Wassermann reaction was negative. A roentgenogram of the skull showed the sella turcica greatly enlarged and destruction of the floor (fig 1). An electrocardiogram showed a rate of 82, left ventricular preponderance, slurred Q R S complex in leads I and II, occasional ventricular premature contractions, inverted P in lead III and inverted T in lead III. Two basal metabolic rates were +7 and +6.

The condition was diagnosed as acromegaly with pituitary tumor and diabetes mellitus with diabetic neuritis and a trophic ulcer

For the first ten days, the patient was given a diet containing 28 Gm of carbohydrate, 43 Gm of protein and 175 Gm of fat (1,920 calories, 71 Gm of glucose²³) For the next five days the diet contained 94 Gm of carbohydrate, 55 Gm of protein, and 242 Gm of fat (2,850 calories, 150 Gm of glucose) Sugar was not found in the urine after the second day The blood sugar on the second day was 237 mg per cent and on the eighth day, 143 mg per cent



Fig 1 (case 1) —Lateral roentgenographic appearance of the skull showing the enlarged sella turcica

CASE 2—Acromegaly of from fifteen to twenty years' duration without signs of pressure and diabetes mellitus without symptoms and of unknown duration

On Jan 20, 1927, a farmer, aged 52, who had lived in Russia until the age of 16, came to the Mayo Clinic complaining of pain in the chest and general weakness The family history was irrelevant He had been married for twenty-six years and had nine children living and well Appendectomy had been performed in 1915, and herniotomy in 1925 A moderate attack of influenza had occurred in 1918 He used coffee and tobacco in moderation He had had a burning pain in the lower substernal region radiating through to the back for four

²³ Glucose value "G" (Woodyatt) = $100 C + 0.58 P + 0.1 F$

years, this had been relieved by eating and drinking, and had not been aggravated by strenuous exertion. There had been periods of freedom from this pain for weeks at a time. He complained also of flatulence and periods of "sour stomach." Vision was poor. There was a slight chronic cough. For three years, exertion had provoked a little more dyspnea than normal. Moderate nocturia had been present for several years. He had been aware of an increase in the size of his face and hands for fifteen or twenty years.

The patient was obese, he was 5 feet 9 inches (175.3 cm) in height, and weighed 213 pounds (97 Kg). The features, hands and feet were typical of acromegaly. Sonorous râles were present at the hilum and the base of the right lung. The axillary lymph nodes were enlarged. The heart was normal except for distant sounds. The blood pressure was 120 systolic and 88 diastolic, the pulse rate was 104 and the temperature 99°F. There was bilateral recurrent inguinal hernia, spermatocele was found on the right. The prostate was moderately enlarged. The right palpebral fissure was larger than the left. Vision was about 6/15 in both eyes, and the visual fields were normal. The vocal cords were thickened and the arytenoids enlarged, suggesting acromegaly.

The specific gravity of the urine was 1.033, and its reaction acid. It contained a trace of albumin, 4.2 per cent sugar, or 51.08 Gm in 1,200 cc (twelve-hour specimen), but no acetone or diacetic acid, the microscopic examination was negative. The blood sugar was 240 mg per cent. The hemoglobin was 87 per cent, the erythrocytes numbered 4,650,000 and leukocytes, 7,800. The Wassermann reaction was negative. The total gastric acidity was 42 and the free hydrochloric acid, 24. Fluoroscopy and roentgenography of the stomach gave negative results. A roentgenogram of the chest was negative except for moderate enlargement of the heart. The sella turcica was normal in size in the roentgenogram. An electrocardiogram showed a rate of 88 sinus rhythm, notched Q R S complex in lead III and left ventricular preponderance.

The diagnosis was acromegaly and diabetes mellitus. The cause of the sub-sternal pain was not determined.

The patient was given a diet containing 100 Gm of carbohydrate, 42 Gm of protein and 153 Gm of fat (2,004 calories, 140 Gm of glucose). Glycosuria was not present while this diet was maintained. The blood sugar on the third day was 180 mg per cent.

CASE 3—Acromegaly with early diminution of glucose tolerance, clinical diabetes later, similar in all respects to ordinary diabetes, increased metabolism responding to rest, latent syphilis

On Oct 15, 1921, a French-Canadian laborer, aged 51, presented himself for examination at the Mayo Clinic, complaining of rheumatic pains in the knees and hoarseness. The family history was irrelevant. He had been married thirty-five years and had one child, aged 21, living and well. The only event of importance in the history was a penile lesion at the age of 20, which had been cauterized. This had been followed by patchy alopecia. During the winter of 1919 and 1920, "rheumatism" of the left knee developed, and in June, 1921, the right knee became similarly affected. In January, 1921 he contracted a severe "cold" which lasted three months. A month after the onset of this cold he became hoarse. The hoarseness persisted but had been somewhat better during the month preceding admission. Aphonia had never been present. There had been some dyspnea during the last month and some obstruction to breathing at night. He had been perspiring excessively for the last two or three months. He had noticed that his hands had been getting larger for two or three months but did not think his feet had increased in size. No one had ever commented on a

change in his appearance, but he thought that his features had become altered, although he had never paid much attention to this. He thought that he had become more stooped.

The patient's skin was hairy, he was 5 feet 6 inches (167.6 cm) tall and weighed 175 pounds (79 Kg). The lower jaw and hands were large, the shoulders stooped and the chest barrel-shaped. He was bow-legged. All of the superficial lymph nodes were moderately enlarged, especially the cervical nodes. The knees creaked on passive motion. Moderate arteriosclerosis was present. The blood pressure was 182 systolic and 115 diastolic, the pulse rate was 94.



Fig 2 (case 3)—Lateral roentgenographic appearance of the basal region of the skull, showing the enlarged sella turcica.

and the temperature, 98.6 F. On the dorsum of the penis was a small scar. Laryngoscopy showed slight edema of the epiglottis and arytenoids with fixation of the left vocal cord in the bilateral abductor position, both vocal cords were reddened. This picture, other than the fixed cord, suggested acromegaly to the laryngoscopist. Vision in the left eye was 6/10 with correction, and in the right, 6/7 with correction. The visual fields were normal except that there was no color field for green or blue, with the 6/280 test object.

The urinalysis was negative. The Wassermann reaction was strongly positive twice. The spinal fluid was normal. The hemoglobin was 77 per cent, the erythrocytes numbered 4,360,000 and the leukocytes, 5,300. Two basal metabolic

tests were + 33 and + 21. A roentgenogram of the skull showed great enlargement of the sella turcica (fig 2). Roentgenograms of the hands and feet were reported positive for acromegaly. A roentgenogram of the chest was negative. The result of a sugar tolerance test after the ingestion of 100 Gm of glucose is recorded in table 1.

The patient was given two courses of six intravenous injections each of arsphenamine, and forty-two intramuscular injections of mercuric succinimide.

On April 21, his condition was the same. He complained of sweating. The Wassermann reaction was positive.

On May 18, the Wassermann reaction was strongly positive.

On Jan 6, 1926, the patient reappeared. He had not received any more antisyphilitic treatment. A year before this examination, polydipsia and polyuria developed, and a qualitative restrictive diet was given with injections of insulin three times a day for two weeks. The thirst and polyuria disappeared for six months and then recurred. He had not restricted his diet for the last few months. Since last seen, he had gained in weight for a time, but during the last year, in spite of a large appetite, he had lost 21 pounds (9.5 Kg). At the time of examination he weighed 162 pounds (73.5 Kg). He complained of slight

TABLE 1—*Sugar Tolerance Test in Case 3*

| Conditions of Test | Blood Sugar, Mg per Cent | Glucose in Urine, per Cent | Amount of Urine, Cc |
|---|--------------------------------|----------------------------------|---------------------------|
| Fasting | 200 | Trace | 150 |
| One half hour after the ingestion of 100 Gm glucose | 230 | Trace | 30 |
| One hour after ingestion of glucose | 240 | 2.5 | 70 |
| Two hours after ingestion of glucose | 230 | 0.16 | 80 |
| Three hours after ingestion of glucose | 180 | Trace | 80 |

intolerance to heat, excessive perspiration and palpitation of the heart. He had been "weak in the knees" for the last five years. There had been loss of libido and potentia for one year. Vision had been somewhat blurred for three months. The additional observations in the physical examination at this time were a small adenoma in the right lobe of the thyroid and a right indirect inguinal hernia. The blood pressure was 136 systolic and 90 diastolic, the pulse rate was 110. There was moderate anemia of the secondary type, the hemoglobin being 68 per cent and the erythrocytes, 3,910,000, this was attributed to hemorrhoids. Vision was 6/20 in each eye, the reduction in acuity probably being due to opacities of the lens, the visual fields were normal. The Wassermann reaction was still strongly positive. Five infected teeth were demonstrated by the roentgen ray. The specific gravity of the urine was 1.041, and the urine contained 5.1 per cent sugar, or 109.1 Gm in 2,140 cc (twenty-four-hour specimen). The basal metabolic rate was +32.

The metabolic rate and the diabetes were studied in preparation for inguinal herniotomy. The patient responded well to the prescribed diet and insulin. Under the influence of rest alone, the basal metabolic rate dropped from +32 to +5. The response to antidiabetic treatment became more satisfactory as the basal metabolic rate fell, but the decrease in the amount of urinary glucose was striking immediately after the institution of injections of insulin. Table 2 is a composite record of the diet, urine, estimation of blood sugar, insulin dosage and basal metabolic readings while the patient's metabolism was being studied, and table 3 is a record of the corresponding data while the diabetes was being studied.

CASE 4—*Somewhat questionable acromegaly of unknown duration, with enlarged sella turcica but without signs of pressure, mild diabetes mellitus of unknown duration and without symptoms, tumor of the spinal cord with operation, necropsy*

On Aug 18, 1925, a Norwegian housewife, aged 68, first appeared at the Mayo Clinic complaining of pain in the left shoulder and numbness of the feet. The family history was irrelevant. She had been married twice, altogether for thirty-five years, and had had three children by her first husband, one of the children had died of tuberculosis and another had died in infancy. Catamenia had been normal, and menopause had occurred at the age of 49. She had not had any previous illnesses but had always been healthy and strong and a hard worker. Several months before examination, she began to notice that her feet felt cold and numb and that later they began to burn and ache. In going upstairs she would stub her toes and often fall. There was no sensation of pain when she struck her toes or bruised her shins. The numbness had increased in severity.

TABLE 2—*First Series of Data Relative to Metabolism (Case 3)*

| Date, 1926 | Diet, Gm | | | Urine | | | | Total Nitrogen, Gm | Blood Sugar, Mg per Cent | Insulin Units | Basal Metabolic Rate |
|------------|--------------|---------|-----|---------------------|-------------------|------------------|-------------|--------------------|--------------------------|---------------|----------------------|
| | Carbohydrate | Protein | Fat | Glucose Equivalent* | Cubic Centimeters | Specific Gravity | Glucose, Gm | | | | |
| 1/ 8 | 109 | 61 | 208 | 255 | 2,210 | 1.012 | 79.22 | 14.14 | 334 | | +32 |
| 1/ 9 | 190 | 62 | 206 | 247 | 2,205 | 1.010 | 135.7 | 13.51 | | | +25 |
| 1/10 | 196 | 65 | 209 | 255 | 2,785 | 1.033 | 145.6 | 13.27 | | | |
| 1/11 | 170 | 63 | 210 | 228 | 2,625 | 1.025 | 119.0 | 11.42 | | | +15 |
| 1/12 | 102 | 63 | 196 | 158 | 2,350 | 1.020 | 69.78 | 10.54 | | | +16 |
| 1/13 | 100 | 58 | 205 | 154 | 1,810 | 1.014 | 20.41 | 9.94 | 364 | 50 | +17 |
| 1/14 | 101 | 67 | 210 | 174 | 1,610 | 1.011 | 3.87 | 7.62 | | 50 | +15 |
| 1/15 | 99 | 58 | 197 | 152 | 1,535 | 1.015 | 6.41 | 8.06 | 250 | 50 | +16 |
| 1/16 | 101 | 62 | 191 | 155 | 1,130 | 1.012 | 0.95 | 7.25 | | 50 | + 8 |
| 1/17 | 101 | 66 | 212 | 160 | 955 | 1.019 | 1.31 | 6.05 | | 50 | |
| 1/18 | 101 | 66 | 208 | 160 | 1,545 | 1.020 | 1.92 | 8.48 | | 50 | + 4 |
| 1/19 | 99 | 62 | 201 | 154 | 2,030 | 1.008 | 1.35 | 6.76 | | 50 | + 7 |
| 1/20 | 101 | 62 | 209 | 157 | 1,705 | 1.015 | 1.57 | | | 50 | — 1 |
| 1/21 | 102 | 62 | 209 | 158 | | | | | | 50 | +10 |
| 1/22 | 100 | 42 | 153 | 140 | | | | | 160 | 50 | + 5 |

* Glucose equivalent $G = 100 C + 0.58 P + 0.1 F$ [Woodruff Arch Int Med 28:125 (Aug) 1921]

She became more and more unable to get about without help. In February she began to have "rheumatic" pains in the left shoulder, which radiated downward around the left side of the thorax to the sternum in front and to the interscapular region behind. The pain was a constant dull ache, which was worse at night. The movements of the arm were not limited. For the last four or five months she had been having trouble occasionally in controlling defecation, especially after the use of a cathartic, the desire to defecate would come suddenly and unannounced. Two months before examination, glycosuria was discovered and a diet was prescribed. Electric therapy had been carried out for the pain in the shoulder without relief. She had not noticed any change in her features or extremities, the onset of the condition had evidently been gradual for a number of years.

The patient was obese, she was 5 feet 4½ inches (163.8 cm) tall and weighed 195 pounds (89 Kg), her normal weight had been 220 pounds (100 Kg). She had typical acromegalic features and hands and feet. The tonsils were chronically infected. The heart sounds were distant, the first apical sound muffled. Moderate arteriosclerosis and hypertrophic arthritis of the terminal joints of the fingers

were present. The left shoulder girdle showed muscular atrophy. Slight edema of the feet and legs was present. The left knee reflex was more active than the right. There was a positive Babinski sign and a suggestive Chaddock response on the left. The pupils were small and sluggish. Vision in the right eye was 6/7 with correction and in the left, 6/6 with correction. The fundi showed mild senile fibrosis. The visual fields were normal. There were a few peripheral lens opacities.

The first urine examined (twelve-hour specimen) contained 7.5 Gm of sugar. The blood urea was 25 mg per cent, the blood sugar 217 mg per cent. The Wassermann reaction was negative. The hemoglobin was 77 per cent, the erythrocytes numbered 4,120,000 and the leukocytes, 5,600. A phenolsulphonphthalein test of renal function gave a return of 40 per cent of the dye in two

TABLE 3—*Second Series of Data Relation to Metabolism (Case 3)*

| Date,* 1926 | Diet, Gm | | | | Blood Sugar Mg per Cent | Insulin Units |
|----------------|-------------------|---------|-----|-----------------------|----------------------------------|------------------|
| | Carbo- hydrate | Protein | Fat | Glucose Equivalent | | |
| 1/24 | 100 | 60 | 208 | 156 | | |
| 1/25 | 100 | 60 | 208 | 156 | | |
| 1/26 | 100 | 60 | 208 | 156 | | |
| 1/27 | 100 | 60 | 208 | 156 | | |
| 1/28 | 100 | 60 | 208 | 156 | | |
| 1/29 | 100 | 60 | 208 | 156 | | |
| 1/30 | 100 | 60 | 208 | 156 | | |
| 1/31 | 100 | 60 | 208 | 156 | | |
| 2/ 1 | 100 | 60 | 208 | 156 | | |
| 2/ 2 | 100 | 60 | 208 | 156 | | |
| 2/ 3 † | 110 | | | | | |
| 2/ 4 | 73 | 35 | 74 | 100 | | 15 |
| 2/ 5 | 73 | 35 | 74 | 100 | | 15 |
| 2/ 6 | 73 | 35 | 74 | 100 | | 15 |
| 2/ 7 | 100 | 42 | 153 | 140 | | 15 |
| 2/ 8 | 100 | 42 | 153 | 100 | | 15 |
| 2/ 9 | 54 | 45 | 206 | 100 | | 15 |
| 2/10 | 54 | 45 | 206 | 100 | | 15 |
| 2/11 | 54 | 45 | 206 | 100 | 130 | 15 |
| 2/12 | 54 | 45 | 206 | 100 | | 15 |
| 2/13 | 54 | 45 | 206 | 100 | | 15 |
| 2/14 | 54 | 45 | 206 | 100 | | 15 |
| 2/15 | 54 | 45 | 206 | 100 | | 15 |
| 2/16 | 54 | 45 | 206 | 100 | | 15 |
| 2/17 | 54 | 45 | 206 | 100 | 147 | 15 |
| 2/18 | 54 | 45 | 206 | 100 | | 15 |

* Glycosuria was not present during this period.

† Herniotomy.

hours (intravenous administration). A roentgenogram of the skull showed moderate enlargement of the sella turcica (fig 3). One of the chest revealed an upper mediastinal shadow, which was diagnosed as a small substernal goiter.

The patient was kept in the hospital for ten days on a diet containing 100 Gm of carbohydrate, 42 Gm of protein and 153 Gm of fat (calories, 2,002, 140 Gm of glucose). The urine remained practically sugar-free on this diet, except for an occasional faint trace. The patient was sent home on a qualitatively restricted diet. The diagnosis was acromegaly, mild diabetes mellitus of the vascular type and suspected tumor of the spinal cord.

On Jan 15, 1927, the pain in the left shoulder and thorax had become more severe and was aggravated by stooping or lifting but not by straining. Weakness of the legs had become more marked, and spasticity had developed, for two months the patient had been completely paralyzed from the waist down and had been confined to bed. During this time muscular atrophy of the legs had developed. The numbness had extended up the legs to a level just above the

umbilicus, and there was almost complete anesthesia in this area to pain and temperature with some reduction of tactile sensation. For the previous month there had been frequent painful flexor spasms of both legs, which would often wake the patient at night. Control of the rectal sphincter had been practically lost, and control of the bladder had become affected later.

The patient weighed 35 pounds (17 Kg) less than on the previous examination. There was practically complete loss of power of the abdominal muscles and of both lower extremities, with spasticity, partial clonus, increased reflexes and definite anesthesia up to the level of the sixth dorsal segment. Tenderness was

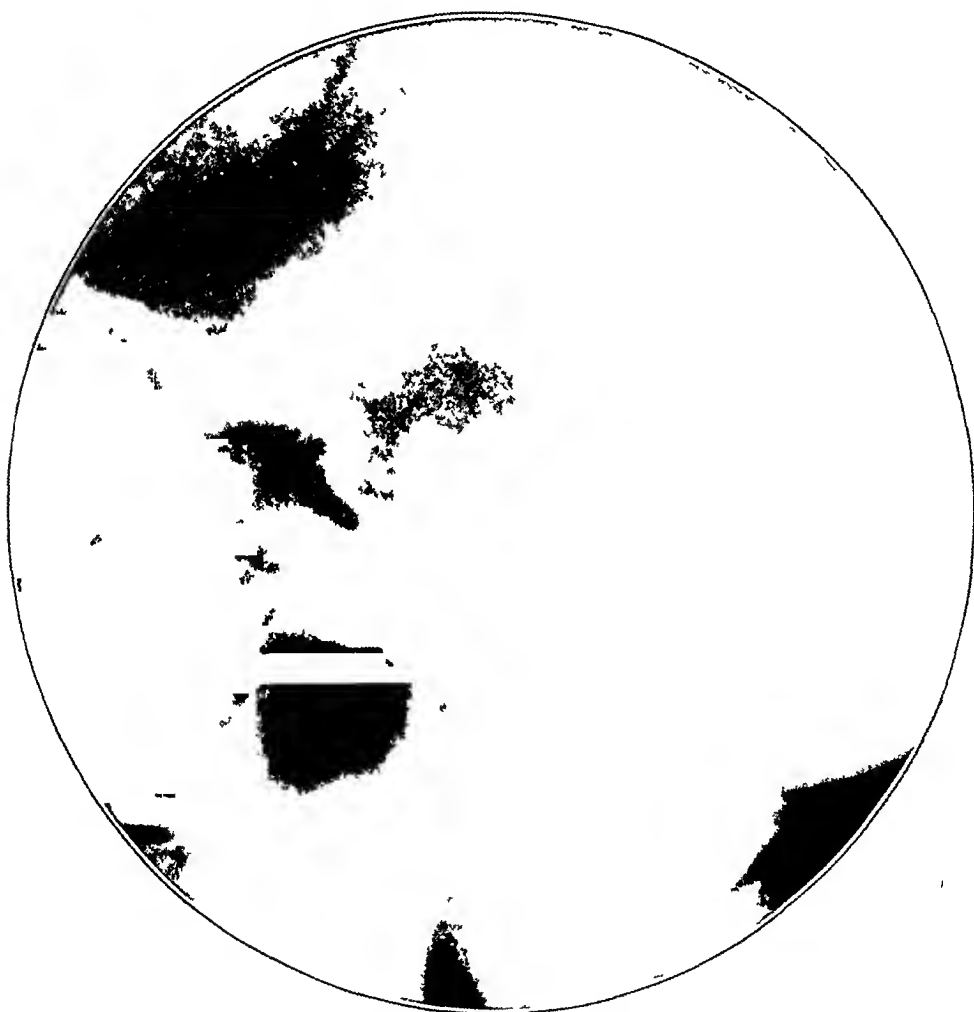


Fig 3 (case 4)—Lateral roentgenogram of the basal region of the skull, showing the enlarged sella turcica

present over the fifth dorsal vertebra. The visual fields were normal. The thyroid was not palpable, although the roentgenogram showed a substernal goiter. The blood pressure was 140 systolic and 88 diastolic, and the pulse rate was 106.

The specific gravity of the urine was 1.031 and the reaction acid, the urine contained a trace of albumin, and 11 per cent, or 4.8 Gm of sugar in 400 cc. The blood urea was 24 mg and the blood sugar, 260 mg per cent. The hemoglobin was 78 per cent, the erythrocytes numbered 4,420,000 and the leukocytes, 4,200. The spinal fluid was slightly yellow, was positive for globulin, contained one lymphocyte to the field, and gave a pressure of 20 cm, there was no

response to jugular pressure. The benzoin sol curve was 000003333332000. A roentgenogram of the spine showed hypertrophic arthritis of the cervical dorsal and lumbar regions.

A tumor of the spinal cord at the level of the fifth or sixth dorsal vertebra was diagnosed and laminectomy decided on. The patient was admitted to the hospital and given a qualitative restriction diet. At the end of five days the blood sugar was 120 mg per cent; there was a trace of sugar in the urine on only two occasions.

On January 26 the patient was taken to the operating room but collapsed following procaine hydrochloride anesthesia and was sent back to her room. She quickly recovered from this condition.

On January 28 there was 21 per cent (19.53 Gm) of sugar in the urine; on January 29, 0.92 per cent (6.58 Gm) and on January 31 only a trace. On



Fig. 4 (case 4).—Small adenoma in anterior lobe of the pituitary gland.
× 60

the same day, under ethylene and ether anesthesia laminectomy of the fourth, fifth and sixth vertebrae was performed. Directly beneath the fifth a hard, fixed tumor was found. The dura was opened and a calcified endothelioma measuring 10 by 18 cm was exposed. It lay posteriorly and to the left and flattened the cord to a mere ribbon. The tumor was removed and the dura closed. The patient's condition was good throughout the operation and the blood pressure was 120 systolic at the end. She regained consciousness but suddenly died later the same day.

The essentials of the pathologic report by J. W. Kernohan are as follows: The pituitary gland was about twice the normal size. It contained large collections of colloid material. The pars intermedia showed glial proliferation. The pars anterior was larger than normal, and throughout its entirety some acini were seen which contained small collections of colloid and stained pale with



Fig 5 (case 4)—Section through the ossified endothelioma of the spinal cord, $\times 60$

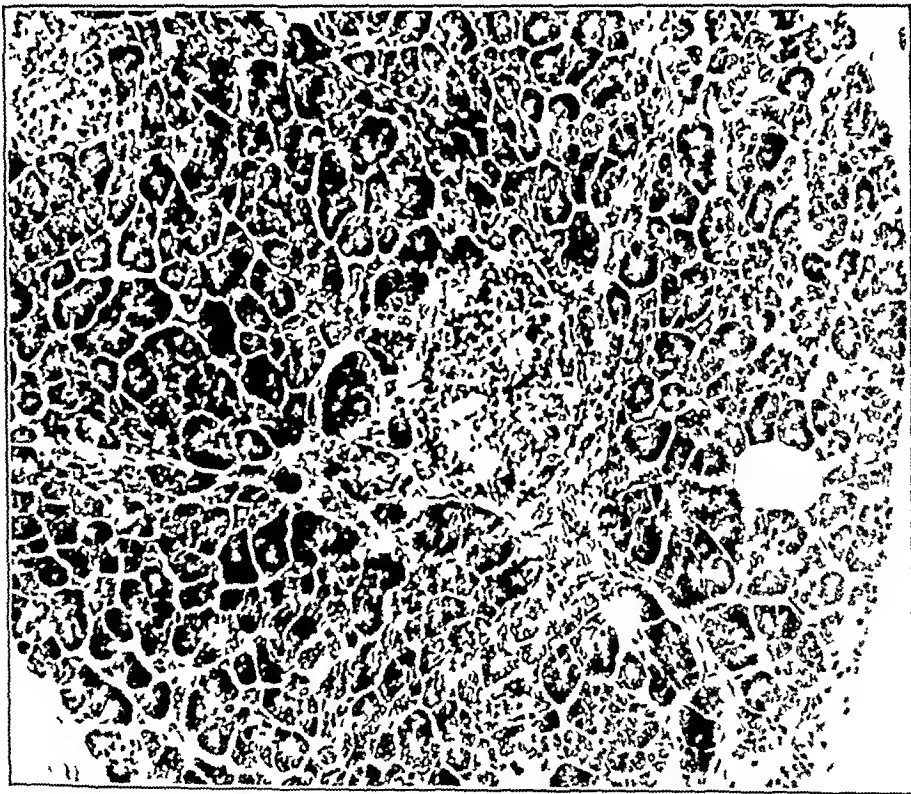


Fig 6 (case 4)—Section through the tail of the pancreas, showing fibrosis and hyalinization of one of the islands of Langerhans, $\times 120$

hematoxylin The majority of the cells were eosinophilic but some were basophilic in reaction There was a small adenoma just beneath the capsule of the pars anterior, composed mainly of eosinophilic cells (fig 4) There were also several small adenomas in the substance of the pars anterior similar to this An occasional mitotic figure was seen throughout the pars anterior

The tumor of the spinal cord was a typical endothelioma, with numerous psammoma bodies and some large areas of ossification with bone marrow spaces containing fat and blood cells (fig 5)

In the head of the pancreas was a considerable degree of replacement of fat The islands of Langerhans were, for the most part, of normal appearance A few showed slight excess of fibrous tissue In the body of the pancreas considerable arteriosclerosis was noted throughout, but the islands did not show



Fig 7 (case 5)—Appearance of patient thirteen years previous to the first examination

notable changes In the tail of the gland the majority of the islands appeared normal, but a few showed fibrosis and hyalinization (fig 6) Excessive fat was observed in sections of the liver stained with scharlach R

CASE 5—Acromegaly of thirteen years' duration with beginning signs of pressure, history of symptoms of hyperthyroidism for five years, diabetes mellitus somewhat atypical, of two years' duration, with two attacks of coma, thyroidectomy and death

On June 1, 1927, a woman, aged 41, presented herself for examination at the Mayo Clinic with the complaint of diabetes The family history was irrelevant She had been married twenty years without the desired pregnancy Menstruation had begun at the age of 13 and had been regular until twelve years before admission, when menopause suddenly occurred at the age of 29, although there was a slight flow once in 1920 She had not been ill except for a mild attack of influenza in 1916 She had been examined previously at the Mayo Clinic in December, 1920 Her complaint then had been puffiness and enlargement of the

acral parts and the face, of six or seven years duration. At first there had been considerable aching in the forearms and hands. She had had to wear gloves and shoes two sizes larger than usual and had gained 20 pounds (9.9 Kg). She felt well except that all work was an effort. For two years there had been a large goitrous swelling in the right side of the neck, but after administration of thyroid extract for fifteen months the size of this was greatly reduced. The skin had previously been dry but had become moist and less puffy. Her appearance was strikingly different from what it had been thirteen years before, as shown by a photograph taken at that time (fig 7). On examination at that time, typical acromegaly was found. The sella turcica was enlarged (graded 4) and the posterior clinoid processes eroded. The visual fields were normal. Glycosuria was not present. Estimation of the blood sugar was not made. Two basal metabolic



Fig 8 (case 5)—*A*, front view of patient as she appeared at the time of the last examination, showing typical acromegalic physiognomy and acromegalic appearance of hands. *B*, side view of same patient.

rates were $+7$ and $+4$. The thyroid gland was not reported as being enlarged. The patient was discharged without medication.

About two years later, symptoms suggestive of hyperthyroidism appeared: nervousness, tremor, intolerance to heat, undue perspiration, excessive appetite and easily induced fatigue. However, there was no loss of weight. These symptoms had persisted for three years when polydipsia and polyuria appeared, the patient then began to lose weight, but the symptoms of hyperthyroidism were greatly ameliorated and she felt better and stronger. Six months after the onset of thirst and polyuria, she suddenly became comatose. Her physician diagnosed the condition as diabetic coma, administered insulin, and after two days she regained consciousness. From then on, she was on a weighed diet containing 50 Gm of carbohydrate, 60 Gm of protein and 130 Gm of fat (98 Gm of glucose), she took ten units of insulin three times a day. The thirst and polyuria

soon disappeared, she felt well, and the puffiness of the features and extremities decreased markedly, so that she was able to wear shoes a size smaller. She gradually lost 29 pounds (103 Kg) in weight. During the year and a half on this regimen, the urine was tested frequently but sugar was never found (However, the Benedict's solution she used was afterward found to be worthless). During this time she did not have more than four or five recognizable reactions to insulin.

About a week previous to examination, June 1, 1927, the patient became nauseated and lapsed into somnolence. The attending physician found large amounts of glucose in the urine, whereupon he administered 300 units of insulin within forty-eight hours. At the end of this time, the patient awoke for half



Fig 9 (case 5) —Lateral roentgenographic appearance of the skull, showing the enlarged sella turcica and the "putty finger" markings of increased intracranial pressure

a day but relapsed into coma. A consultant was called from the Mayo Clinic, and he decided that she had been revived from impending diabetic coma only to go into a state of hypoglycemic shock. He administered 20 Gm of glucose intravenously, and she recovered. The patient resumed her former diet, but took fifteen units of insulin instead of ten units three times a day. During five days with this dosage there was only one insulin reaction and the urine was sugar free.

At this time the appearance of the patient was about as it had been seven years before, large nose, prognathism, puffy eyelids, large fissured tongue, widely separated teeth, large spade-like hands and feet and genu varum (fig 8). The skin, however, was only slightly thicker than normal. She was 5 feet 2 inches

(157.5 cm) tall and weighed 133 pounds (61 Kg). The thyroid gland was enlarged, the right lobe measuring about 3.5 by 6 cm and the left about 2.5 by 5 cm, definite nodules were not palpable, and bruits were not audible. There was slight tremor of the fingers but no weakness of the quadriceps muscles. The heart was slightly enlarged to the left, with a faint systolic murmur over the precordia. There were several rows of flat brownish verrucae about the torso below the costal margin. The finger nails were small and triangular, with longitudinal striations and absence of the crescents. The uterus was small and atrophic. The blood pressure was 104 systolic and 68 diastolic, the pulse rate 80 and the temperature 99 F. Vision in the right eye was 6/12 with correction and in the left, 6/60 with correction. The left temporal field was slightly contracted, and the left optic disk somewhat pale.

The first urine examined did not contain sugar and had a specific gravity of 1.006 (the patient was on a diet and was taking insulin). The blood sugar was

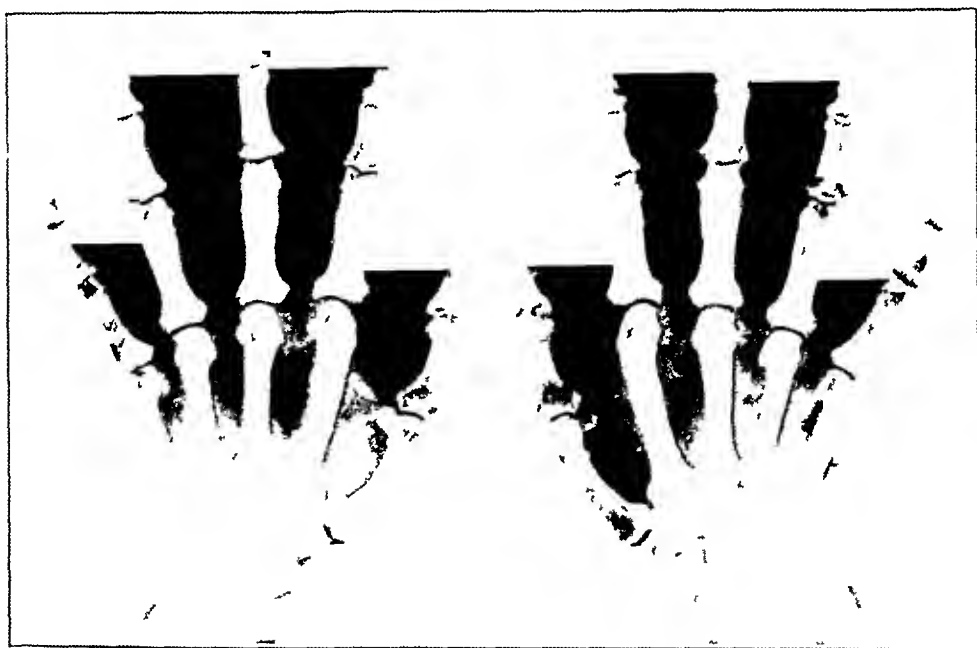


Fig 10 (case 5)—Bony overgrowth of the phalanges and tufting of the distal ends of the terminal phalanges

173, blood urea 10 mg per cent and the carbon dioxide combining-power, 63 volumes per cent. The hemoglobin was 87 per cent, the erythrocytes numbered 4,660,000 and the leukocytes 4,500. The Wassermann reaction was negative. A roentgenogram of the skull showed that the sella turcica was about as before, but that there was now also evidence of marked increased intracranial pressure (fig 9). Roentgenograms of the teeth showed periapical infection in all of the lower and in five of the upper teeth. Roentgenograms of the hands revealed overgrowth of bone of the phalanges and typical acromegalic tufting of the distal ends of the terminal phalanges (fig 10).

Table 4 shows the daily estimations of sugar, and nitrogen in the urine, blood sugar, insulin dosage, basal metabolic records and dosage of compound solution of iodine (Lugol's solution) for the period of three and a half weeks in the hospital. During this time, the patient was getting a weighed diet containing 77 Gm of carbohydrate, 50 Gm of protein and 140 Gm of fat (1,768 calories, 120 Gm of glucose).

On June 10, the estimations of blood sugar and urinalyses were made after a period of fasting and at intervals of half an hour up to noon after a breakfast containing approximately 40 Gm of available glucose. The results are recorded in table 5. These figures show merely that the renal threshold for glucose was at least not lower than 0.155 mg of glucose for each hundred cubic centimeters of blood.

Six estimations of the respiratory quotient during the first two weeks were 0.82, 0.83, 0.81, 0.81, and 0.82, showing theoretically, at least, utilization of glucose.

Three basal metabolic rates before administration of iodine were +31, +27, and +32, and on the seventh, eighth, tenth, seventeenth and nineteenth days of administration of 30 minims (1.9 cc) of compound solution of iodine daily in three doses of 10 minims (0.6 cc) each, +26, +20, +21, +19 and +20.

TABLE 4—Data Relative to Metabolism and Treatment (Case 5)*

| Date, 1927 | Urine Glucose, Gm | Urinary Nitrogen, Gm | Fasting Blood Sugar, Mg per Cent | Insulin Units | Compound Solu- tion of Iodine (Lugol's Solution) Minims | Basal Metabolic Rate |
|---------------|-------------------------|----------------------------|--|------------------|---|----------------------------|
| 6/1 | | | 173 | 10-10-10 | | +31 |
| 6/2 | Trace | | | 10-0-10 | | |
| 6/3 | 11.9 | | | None | | +27 |
| 6/4† | | | | None | | |
| 6/5 | Trace | | | 0-0-10 | | |
| 6/6 | | | | 10-0-10 | 20 | |
| 6/7 | | | | 10-0-10 | 30 | +32 |
| 6/8 | | | 146 | 10-0-10 | 30 | |
| 6/9 | 15.9 (?) | | | 10-0-10 | 30 | |
| 6/10 | | | | None | 30 | |
| 6/11† | | | 155 | None | 30 | |
| 6/12 | | 5.89 | | None | 30 | +26 |
| 6/13 | | 4.05 | 135 | None | 30 | +20 |
| 6/14 | | 1.56 | 137 | None | 30 | |
| 6/15 | 3.35 | 4.1 | 169 | None | 30 | +21 |
| 6/16 | | 3.54 | 165 | None | 30 | |
| 6/17 | | 1.7 | 167 | None | 30 | |
| 6/18 | | | 155 | None | 30 | |
| 6/19 | | | | None | 30 | |
| 6/20 | | 1.12 | 142 | None | 30 | |
| 6/21 | Trace | 3.07 | 144 | None | 30 | |
| 6/22 | | 1.4 | | None | 30 | +19 |
| 6/23 | Trace | 6.56 | | None | 30 | |
| 6/24 | | | 144 | | 30 | +20 |

* During the period in which these records were made, the diet contained 77 Gm of carbohydrate, 50 Gm of protein and 140 Gm fat (1,768 calories, available glucose, 120 Gm).

† Sunday, tests not made.

H. S. Plummer diagnosed the condition as hyperfunctioning adenomatous goiter, and advised thyroidectomy. It was decided, however, to treat the pituitary gland with roentgen rays first to determine whether the basal metabolic rate could be lowered by this means and thus to determine whether there was a relationship between the pituitary condition and the increased metabolism. Accordingly, three treatments were given and the patient dismissed with instruction to take 10 minims of compound solution of iodine daily and to return for reexamination in six weeks.

During this period at home, the patient adhered strictly to the weighed diet. She examined the urine daily for sugar and found it normal except on a few occasions when the reaction indicated slight reduction, at such times, she took 5 units of insulin. Subjectively, she was much better.

On Aug. 5, 1927, she returned to the clinic. The first twenty-four-hour specimen of urine produced complete reduction, but the following day only a

trace of sugar was present. The blood sugar was 325 mg per cent. Two basal metabolic rates were +36 and +47.

Partial thyroidectomy was performed (Pemberton) on August 13. The right lobe was enlarged to about four times the normal size. Three fourths of this lobe was removed, but the left lobe, being normal in size, was not removed. The pathologist reported multiple, small, hemorrhagic, fibrous, calcareous, degenerating colloid and fetal adenomas in a colloid thyroid.

Immediately after operation, the pulse rate jumped to 138 and gradually increased to 178 at the time of death nine days later. There was moderate elevation of temperature, which subsided on the fourth day and then gradually climbed to 105.5 at the time of death. The patient perspired profusely and became more and more restless. She slept a great deal but could easily be aroused. During the last two days before death, she was semidelirious. Administration of iodine was discontinued after operation for three days and then resumed, 30 minims of compound solution of iodine being given daily. Table 6 shows the daily amount of sugar in the urine, the presence or absence of diacetic acid and acetone in the urine, blood sugar, carbon dioxide combining-power of the blood, insulin dosage and amount of glucose and sodium bicarbonate administered from the second day before operation until death. Necropsy was refused.

TABLE 5—*Repeated Estimation of Sugar in Blood and Urine (Case 5)*

| Time | Blood Sugar, Mg | Urine,* Cc |
|-------------------------|-----------------|------------|
| 8 00 a m | 0 118 | 10 |
| Breakfast, 8 15 to 8 30 | | |
| 9 00 | 0 140 | 300 |
| 9 30 | 0 120 | 275 |
| 10 00 | 0 155 | 75 |
| 10 30 | Blood clotted | 50 |
| 11 00 | 0 140 | 75 |
| 11 30 | 0 112 | 25 |
| Noon | 0 142 | 175 |

* Sugar was not found in the urine at any time.

CASE 6—*Acromegaly of many years' standing without signs of pressure, diabetes mellitus of seven years' duration, increased metabolism, adenomatous thyroid gland*

On Aug 22, 1927, a steel worker, aged 44, came to the Mayo Clinic because of diabetes mellitus. The family history and early personal history were unimportant. Seven years previously, weakness, polyuria, polydipsia and polyphagia had appeared. The condition was diagnosed as diabetes mellitus and the diet loosely restricted qualitatively in carbohydrates. A year later he began to take insulin and during the last two years had often taken as much as 160 units in a day without severe reaction. Five or six years before admission, the patient complained of nervousness and palpitation. Three years before admission, headaches began and became almost constant, they were mainly frontal and temporal. Attacks of dizziness recurred at irregular intervals and sometimes caused the patient to fall to the ground but without loss of consciousness. Diplopia was present on several occasions, and a slight degree of photophobia persisted. Thickness of speech had been present for two years. Two years previously, all of the teeth had been extracted and following this the patient complained of weakness of the left side which gradually disappeared in the course of three months. This had been attributed to cerebral embolism. Sexual desire was completely lost. For two years he had been unable to work because of weakness

The patient stated that he had not noticed any alteration in his features, but his brother asserted that they had become coarse in the last few years. From comparison with an old photograph, it was evident that the features had actually undergone a distinct change during the last twenty years. The patient recalled that he had been wearing a larger hat during the last ten years.

The patient was 5 feet 6 inches (167.6 cm) tall and weighed 180 pounds (82 Kg). The features were typical of acromegaly, the skin coarse, and the hands and feet large. A small adenoma, less than 1.0 cm in diameter, was palpable in the right lobe of the thyroid gland. A moderate degree of weakness of the quadriceps, slight tremor of the fingers and some undue sweating were present. The tonsils were moderately enlarged and contained soft plugs. The teeth were artificial. Vision was normal, and the visual fields and ocular fundi did not show any significant changes. The blood pressure was 148 systolic and 90 diastolic, the pulse rate ranged constantly around 100, and the temperature was 98 F.

TABLE 6—Laboratory and Therapeutic Data Before and After Thyroidectomy (Case 5)

| Date, 1927 | Amount of Urinary Glucose, Gm | Urinary Diacetic Acid | Urinary Acetone | Blood Sugar, Mg per Cent | Carbon Dioxide Combining Power, per Cent by Volume | Insulin Units | Glucose Equivalent With Diet, Gm | Sodium Bicarbonate Intravenously, Gm |
|------------|-------------------------------|-----------------------|-----------------|--|--|---------------|----------------------------------|--------------------------------------|
| 8/11 | 10.4 | | | | | | 140 | |
| 8/12 | | | | | | | 120 | |
| 8/13* | 13.5 | | + | 392 | | 20 | 50 | |
| 8/14 | 49.7 | | + | | | 30 | 75 | |
| 8/15 | 87.0 | + | + | 350 | | 30 | 120 | |
| 8/16 | 84.3 | + | + | 400 | 29 | 90 | 118 | 45 |
| 8/17 | 124.6 | + | + | 400 | 38 (8 a m) 37 (2 p m) | 80 | 133 | |
| 8/18 | 58.9 | + | + | 426 | 30 | 135 | 127 | 25 |
| 8/19 | 64.5 | + | + | 454 (8 a m) 454 (2 p m) 454 (4 p m) | 30 | 215 | 120 | |
| 8/20 | 27.3 | | | 500 | 51 | 160 | 120 | |
| 8/21 | | | | | | 20 | 25 | 25 |

* Thyroidectomy

The urine had a specific gravity of 1.032 and contained a moderate amount of albumin and sugar. The blood sugar was 206 mg per cent. The Wassermann reaction was negative. The hemoglobin was 74 per cent, the erythrocytes numbered 4,260,000 and the leukocytes, 10,900. A roentgenogram of the chest revealed a small substernal goiter, and one of the skull showed enlargement of the sella turcica with thinning of the posterior clinoid processes. Two basal metabolic rates taken before the administration of iodine were +28 and +27, and after the patient was given compound solution of iodine (30 minims daily for seven days) the rate was +30.

The patient was kept in the hospital for two weeks on a diet containing 65 Gm of carbohydrate, 50 Gm of protein and 260 Gm of fat (2,790 calories, 120 Gm of glucose). Traces of sugar appeared in the urine on this diet, and 10 units of insulin twice daily was required to keep the urine sugar free. On the diet alone the blood sugar dropped to 165 mg per cent. The patient's condition improved considerably under treatment. Thyroidectomy was considered, but the patient decided to wait for a while before operation.

COMMENT

The six cases reported demonstrate the similarity of "acromegalic diabetes" to ordinary diabetes mellitus. Polyuria and polydipsia were present in the more severe forms of diabetes and were proportionate to the intensity of the disease. Cases 1 and 3 illustrate the point made previously that the incidence of the association of diabetes and acromegaly may be greatly underestimated. In case 1, the diabetes was mild and readily controlled by diet. If this patient had been examined at a time when she was eating sparingly of food containing carbohydrate the glycosuria would not have been discovered and the diabetes would have passed unrecognized in the absence of an estimation of blood sugar, as there was evidently a high renal threshold for glucose. In case 3, the urine was free from sugar three years before the clinical appearance of diabetes, but the fasting blood sugar was 200 mg per cent and a diabetic glucose tolerance curve was obtained at that time.

Three of the cases were readily controlled by diet alone, and the other 3 required insulin as well. The response to insulin was just as striking as in any case of diabetes. From table 2, it is apparent that in case 3 the response to antidiabetic treatment became more satisfactory as the basal metabolic rate fell to normal under the influence of rest. Wilder emphasized the influence of hyperthyroidism with its increased metabolism on the severity of diabetes. This observation however, does not detract from the validity of the effect of insulin in this case, since there was an immediate and marked decrease in the urinary glucose after the administration of insulin. In case 5 (table 4), it was possible to keep the diabetes under control without insulin after the basal metabolic rate began to fall under the influence of iodine. That improved tolerance results from the administration of iodine to persons with combined exophthalmic goiter and diabetes has been shown by Boothby²⁴ and Wilder.

Apparently, there have been few patients with "acromegalic diabetes" who have been carefully treated with insulin. Colwell⁵ recently reported a patient who had acromegaly with diabetes who responded to insulin in a manner similar to that observed in ordinary diabetes. Blum and Schwab²⁵ compared the blood-sugar curves after the administration of 30 units of insulin in a case of diabetes unassociated with acromegaly and in one associated with that disease and observed

24 Boothby, W. M., and Wilder, R. M. Metabolism Studies in Exophthalmic Goiter Complicated by Diabetes, *J. Clin. Investigation* **1**:590, 1924-1925.
Wilder, R. M. Hyperthyroidism, Myxedema and Diabetes, *Arch. Int. Med.* **38**:736 (Dec.) 1926.

25 Blum, L., and Schwab, H. Diabète acroméganique et insuline, *Compt. rend. Soc. de biol.* **89**:195, 1923.

a similar reduction curve in both. After the administration of insulin, one of John's patients responded as expected, but a weighed diet was given at the same time so that the exact effect of the insulin is not certain. This case was extremely interesting, as the blood sugar and glucose tolerance were normal three months later, although the diet during that time had been liberal. In a recent article, Davidoff and Cushing²⁰ concluded that "insulin will control acromegalic diabetes but far less effectively than it does the more common forms of diabetes unassociated with hyperpituitarism, the assumption being that the increased pituitary activity tends to counteract its effects," but they did not bring out striking or convincing evidence on this point, describing only a case in which the blood sugar apparently was not much affected by insulin until after a "generous portion of his pituitary adenoma was removed." Furthermore, they had previously remarked, "three of our patients with acromegalic disease had been shown to respond normally to insulin." So far, the balance of evidence at hand from a clinical standpoint certainly favors the deduction that insulin acts in "acromegalic diabetes" just as it does in diabetes without acromegaly.

While it is not my object in this paper to discuss particularly the question of the rate of metabolism in acromegaly or the much debated question of the possible interrelationship between the pituitary and thyroid glands, a few words in this regard would not be amiss, since 3 of these patients (cases 3, 5 and 6) presented the interesting combination of acromegaly, diabetes mellitus and increased metabolism.

In case 3, there was an elevation of the basal metabolic rate which gradually dropped to normal during a rest period of two weeks. There was a palpable adenoma of the thyroid gland, and some symptoms suggested hyperthyroidism. The history indicated that the diabetes was greatly aggravated about the time that the latter symptoms became manifest. However, "the recognition of mild grades of hyperthyroidism is often a difficult matter, and in the presence of diabetes it becomes doubly difficult owing to the fact that certain symptoms, notably bulimia, loss of weight and weakness, are common in both conditions" (Wilder).

The history in case 5 suggests that the onset of hyperthyroidism took place five years before the second examination at the Mayo Clinic and that the diabetes began three years after the onset of the hyperthyroidism. The patient may have been on the crest of a wave of hyperthyroidism at the time of the first attack of coma and again later with the attack of impending coma. This possibility, however, is not clearly ascertainable from the history. It is also difficult to explain the improvement in the symptoms of hyperthyroidism with the onset of the diabetes, a point on which the patient insisted. Likewise, the definite improvement in the acromegaly after the onset of the diabetes

is inexplicable. If it had occurred with the onset of the symptoms of hyperthyroidism, it could have been due to the disappearance of previous myxedema complicating the acromegaly. The reason for this patient's death after partial thyroidectomy is difficult to explain. The picture did not resemble any other known condition. There was not sufficient acidosis to cause death, in fact, it was under control the preceding day.

Thyroid crisis would explain the inability of insulin to affect the blood sugar, but thyroid crisis is incompatible with the histologic picture of the gland. The cause of death in this case will probably always remain a mystery. In general, acromegaly is regarded, without any definite reason, as increasing the surgical risk.

In case 6 there is a likelihood that the diabetes was precipitated or at least aggravated by the onset of hyperthyroidism, although the time relations are not very clear. In this case there were many mild symptoms of hyperthyroidism, and a small adenoma was palpable in the gland.

In 1897, Magnus-Levy²⁶ called attention to such symptoms as cardiac hypertrophy, exophthalmos, tachycardia and sweats in patients with acromegaly. The experiments of Crowe, Cushing and Homans²⁷ in 1910 showed that adiposity, lethargy and subnormal temperature followed hypophysectomy in young animals. In 1927, Cushing and Davidoff²⁸ reported that in 45.8 per cent of 72 cases of acromegaly the basal metabolic rate was above $+10$ and also that in 25 of 100 cases of acromegaly the thyroid was palpable or definitely enlarged, in 17 of these reliable studies of the basal metabolic rate were made, and in 15 it was found to be elevated. However, in 75 per cent of the cases in which the rate was definitely elevated, the thyroid gland was not even palpable. In contrast with these observations, the basal metabolic rate in 58 proved cases of hypopituitarism was below -10 . Thyroidectomy in some of these cases served to lower the basal metabolic rate and iodine was shown also to lower it, although the gland in the three cases in which operation was performed showed merely colloid changes of adenomatous type "without expected evidence of toxicity." On the other hand, operations on chromophilic adenoma of the pituitary gland with elevated basal metabolic rate not associated with palpable enlargement of the thyroid were followed by a uniform and striking fall in the basal metabolic rate. Cushing and Davidoff²⁸ concluded

26 Magnus-Levy, A. Untersuchungen zur Schilddrüsensfrage, *Ztschr. f. klin. Med.* **33** 269, 1897.

27 Crowe, S. J., Cushing, Harvey, and Homans, John. Experimental Hypophysectomy, *Bull. Johns Hopkins Hosp.* **21** 127, 1910.

28 Cushing, Harvey, and Davidoff, L. M. Studies in Acromegaly. IV. The Basal Metabolism, *Arch. Int. Med.* **39** 673 (May) 1927.

that the chromophilic cells of the anterior lobe of the pituitary gland secrete a substance which not only contains the hormone of growth but which is capable of raising the basal metabolic rate, and that whether it acts as a stimulus to metabolism directly on the tissues or only through intermediation of the thyroid gland cannot as yet be definitely stated

Of the 79 cases of acromegaly in the series from the Mayo Clinic, the thyroid gland was definitely abnormal by palpation in 34 (43 per cent) The basal metabolic rate was determined in 57 of the 79 cases Of these 57, there were 29 in which the basal metabolic rate was above $+10$, however, in 13 of these the examination was made in the earlier days, and only one rate was determined In 3 cases not showing evidence of goiter or hyperthyroidism, the rate was elevated, in one of these, seven determinations varied between $+53$ and $+30$ In none of the 57 in which the rate was estimated was it below -10 , and in only 4 was it between zero and -10 It is definitely established, therefore, that both abnormal thyroid glands and increased metabolism are common in cases of acromegaly What relation there is between the two glands is difficult to decide on the present data

Case 4, while not a cleancut example of acromegaly, was sufficiently suggestive and interesting to be included in this report The tumor of the spinal cord was extremely interesting, it was a typical endothelioma but the large areas of ossification with bone marrow are unusual If one should consider this a case of acromegaly, it would afford interesting speculation to associate the growth of bone tissue in the tumor with hyperactivity of the pituitary gland The observation at necropsy of the degenerative changes in the islands of Langerhans, found mainly in the tail of the pancreas, while interesting, do not throw any light on the relationship of the diabetes to the pituitary hyperplasia Few references have been made to changes in the islands of Langerhans in "acromegalic diabetes" Some of the early necropsy reports mention pancreatic lesions, but they usually consisted of interlobar fibrosis, the islands being apparently normal A few references have been made, however, to the occurrence of significant microscopic changes in the islands, some writers have cited instances of atrophy, hyperplasia, fatty degeneration, hyalinization or sclerosis of the islands, but many of these were in cases of acromegaly without diabetes Norris²⁹ described adenomatous hypertrophy of the pancreatic islets in a case of acromegaly with diabetes Kraus³⁰ reported sclerosis of the islands

²⁹ Norris, C A Case of Acromegalia, Proc New York Path Soc 7 19, 1907-1908

³⁰ Kraus, E J Die Beziehungen der Zellen des Vorderlappens der menschlichen Hypophyse zueinander unter normalen Verhältnissen und in Tumoren, Beitr z path Anat u z allg Path 58 159, 1914

in another case Cushing and Davidoff³¹ reported on the condition of the islets in two cases of acromegaly and diabetes in one, in which the glycosuria had disappeared, there was an increase in the number and hypertrophy of the islets, in the other, after death in diabetic coma, the islets were normal (except for a single island which was slightly sclerosed). The frequent absence of demonstrable changes in the islands in cases of diabetes unassociated with acromegaly is well known. The accepted theory of diabetes as a disorder of the islands of Langerhans has found meager substantiation from the anatomic standpoint.

SUMMARY

A brief summary of the results of the main experimental and clinical investigations on the question of the relationship of the pituitary gland to carbohydrate metabolism has been given. Six more cases have been recorded of the interesting combination of acromegaly and diabetes mellitus, in 3 of which insulin was required. In 1 of these cases, the diagnosis of acromegaly is admittedly questionable. Four others of a series of 79 cases of acromegaly showed some disturbance of carbohydrate metabolism, but this feature was not carefully studied in them. The diabetes in the 6 cases reported was in all essential respects similar to the ordinary form and responded similarly to diet and insulin therapy. Three of the patients presented the unique complication of increased basal metabolic rate, in all three of whom it was presumably due to hyperthyroidism.

CONCLUSIONS

1. The assumption that the diabetes associated with acromegaly is due to the same cause which produces the acromegaly derives its main support from the following points: (1) Acromegaly (hyperpituitarism due to chromophilic hypophyseal adenoma) is frequently associated with diabetes mellitus, (2) The syndrome of hypopituitarism (due to chromophobe hypophyseal adenoma) is infrequently associated with diabetes mellitus, (3) even though hypophysectomy in man has never been followed by a cure of the diabetic condition, it has been followed by a state of increased sugar tolerance, as shown in a few instances by the intravenous tolerance test, this increase in tolerance has been demonstrated even when clinical diabetes did not exist, (4) even though clinical diabetes may not be present, glucose tolerance may be diminished in cases of acromegaly, as shown in a few instances by the intravenous tolerance test, (5) transient hyperglycemia and glycosuria may be produced by the injection of pituitary extracts, and (6) pituitary

³¹ Cushing and Davidoff (footnote 1, second reference)

extract is capable of preventing or relieving hypoglycemia and convulsions produced by injection of insulin

2 The only difference between diabetes alone and diabetes associated with acromegaly is its occasional spontaneous temporary or permanent disappearance, a point which has been demonstrated in relatively few cases

3 It would seem to be most plausible, then, to assume that the diabetes occurring with acromegaly is due to the same factor producing ordinary diabetes, namely, an insufficient production of insulin, although it is possible that enough insulin might be secreted but might be neutralized by some new substance

4 The relation of the hypophysis to carbohydrate metabolism is still far from settled, but there is no doubt of the existence of a relationship

STOMACH TONUS AND PERIPHERAL LEUKOCYTE COUNT (SPLANCHNOPERIPHERAL BALANCE) ^k

SERGIUS ARQUIN, M D

CHICAGO

For a long time it has been known that there is a definite correlation between the peripheral leukocyte count and the various phases of digestion. During recent years, this subject has been investigated with greater interest in relation to functional pathology of the liver (Widal's hemoclastic crisis).

In a series of leukocyte counts on eighty normal persons, Feinblatt ¹ has shown conclusively that following the ingestion of even a small quantity of food a distinct increase in the peripheral leukocyte count resulted within from one to one and one-half hours. Bien and Variekamp, ² taking counts at more frequent intervals, have shown the details of this postprandial curve. Immediately after ingestion there is a fall in the count, within from ten to twenty minutes, this is followed by a slight rise back to normal or slightly above it. For the next thirty to fifty minutes, the leukocyte count is low—below the starting point—and after this period of depression, it rises in the true digestive leukocytosis.

Numerous observers have found that children show a more marked leukopenia than adults, and in those cases which are followed by alimentary leukocytosis (which is not constant in children), the count shows a greater percentage of increase than is true in adults.³

The question of the relation of the type of food ingested to the leukocyte count has also been worked out, chiefly in relation to the hemoclastic crisis. Although some observers report a difference with the types of food,⁴ the majority feel that the variations in both quantity and quality of the material ingested show little if any effect on the number of white cells in the peripheral blood.

In pathologic conditions, especially in relation to disorders of the liver, as Widal first pointed out, there appears to be some disturbance

¹ From the Department of Pathology of the College of Medicine, University of Illinois, Laboratory of Dr. W. F. Petersen.

¹ Feinblatt, H. M. Alimentary Leukocytosis in Eighty Normal Men, *J. A. M. A.* **80** 613 (March 3) 1923.

² Bien, S., and Variekamp, H. *J. Exper. Med.* **36** 415, 1924.

³ Glaser, F. *Med. Klin.* **18** 331, 1922. Abel, E., and Brenas, P. *Compt. rend. Soc. de biol.* **86** 1040, 1922. Mautner, H., and Cori, G. *Klin. Wchnschr.* **1** 523, 1922. Misasi, M., and Aiello, G. *Pediatric*, Naples, **30** 408, 1922. Muriac, P. *J. de med. de Bordeaux* **92** 375, 1921. Schippers, J., and de Lange, C. *Nederl. Tijdschr. v. Geneesk.* **66** 894, 1922.

⁴ Brodan, P., and Sangerons, F. *Presse med.* **26** 124, 1918.

of the regulatory balance. The conviction has grown, however, that this is by no means a peculiarity of hepatic disorders.⁵

The explanations for the leukocytosis following ingestion of food are manifold. Goodall and Paton⁶ believe that the phenomenon results from an increased function of the bone marrow, with an actual increase in the number of cells at the time of digestion. Pohl,⁷ Erdely⁸ and Hofmeister⁹ gave a similar explanation, but felt that the source of the cells was in the lymph glands of the intestine. From¹⁰ advanced the theory that the increased count in the periphery was not an indication of an actual increase in the number of cells, but was more in the nature of a mechanical transportation to the periphery. Viale and Di Leo Lira,¹¹ on the basis of their experiments, attribute this leukocytosis to the increase in the hydrochloric acid in the blood that they found during digestion.

WIDAL'S HEMOCLASTIC CRISIS

Still more numerous than the theories that account for the normal postprandial leukocytosis are the theories for the leukopenia that occasionally is found (Widal's hemoclastic crisis). Widal believes that this leukopenia is evidence of functional proteopexic hepatic deficiency, resulting in a symptom complex in which this condition, while the most easily obtained, is far from the most important. The theory that the phenomenon results from some abnormal mechanical transportation of the leukocytes has some supporters.¹²

Recently, a number of articles have been published in support of the possibility of an autonomic control of the peripheral leukocyte count and, consequently, an derangement of this system in those cases which show an abnormal response to stimulation.

Articles by Widal,¹³ Muller and Petersen,¹⁴ Tincl and Santenose¹⁵ are included in this list. Goudsmit¹⁶ agrees as far as autonomic control

5 Feinblatt, H. M. Alimentary Leukocytosis in Various Pathologic Conditions, *Arch. Int. Med.* **33** 210 (Feb.) 1927. Holzer, P., and Schilling, E. *Ztschr. f. klin. Med.* **93** 302, 1922.

6 Goodall, A., and Paton, D. N. *J. Physiol.* **33** 20, 1905.

7 Pohl, J. *Arch. f. Exper. Path. u. Pharmacol.* **20** 426, 1886.

8 Erdely. *Ztschr. f. Biol.* **46** 31, 1889.

9 Hofmeister, F. *Arch. f. Exper. Path. u. Pharmacol.* **22** 306, 1887.

10 From, G. *Compt. rend. de Soc. de biol.* **53** 311, 1907.

11 Viale, S., and Di Leo Lira, J. *Compt. rend. de Soc. de biol.* **96** 228, 1927.

12 Worms, W. and Schrieber, H. *Ztschr. f. klin. Med.* **93** 323, 1922.

13 Widal, F., Abrams, P., and Lancovescio, N. *Presse med.* **28** 893, 1920.

14 Muller, E. F. *Munchen med. Wchnschr.* **51** 1753, 1922. Muller, E. F., and Petersen, W. F. *Klin. Wchnschr.* **6** 848, 1927.

15 Tincl, J., and Santenose, D. *Compt. rend. de Soc. de biol.* **85** 715, 1921.

16 Goudsmit, J. *Nederl. Tijdschr. u. Geneesk.* **65** 41, 1922.

is concerned, but suggests further that the probable disturbance is in the balance of the blood colloids resulting from a deficiency in the liver. Glaser,¹⁷ on the other hand, believes that the stimulating factors are the bile acids, and that their retention in hepatic deficiency is the probable explanation for the leukopenia and the changes in the blood that Widal has described. Holzer and Schilling¹⁸ find that usually those cases which show gastric anacidity show a typical Widal curve, and they believe that the phenomena are in some way connected. Wollheim¹⁹ has found that the variations in leukocytosis show a definite relation to the potassium calcium ratio of the blood, and can be modified by stimulation of the splanchnic and vagus nerves.

There must be some simple factor which will determine the leukocytic reaction of the periphery and the splanchnic region after the ingestion of food. Any explanation must give due regard to the following known phenomena:

- 1 There is a definite relation to alimentation, this relation being expressed in a series of actions and reactions (to correspond with the fluctuations of the peripheral count before the actual onset to digestive leukocytosis).

- 2 There is more or less uniformity in reaction to the different types of food.

- 3 There is greater instability and susceptibility in the reaction of children than adults.

- 4 Liver disease, asthma, anacidity and similar conditions will modify this factor.

SPLANCHNOPERIPHERAL BALANCE

Considerable work has been done recently as regards an autonomic balance between the periphery and the viscera. It has been shown²⁰ that during a chill, many of the phenomena are accounted for by the fixation of the autonomic system in one direction—the skin and the central organs showing opposite orientation. The liver, the spleen and the gastro-intestinal system all take a distinct part in this process. At the time of the chill, of course, the periphery is in a state of functional inhibition, and the leukocyte count is low. Undoubtedly, therefore, it is possible through the autonomic nervous system to affect a modification of the leukocyte count in the periphery.²¹

¹⁷ Glaser, F. *Med Klin* **18** 688, 1922.

¹⁸ Holzer, P., and Schilling, E. *Berl Klin Wchnschr* **58** 1352, 1921.

¹⁹ Wollheim, E. *Ztschr f d ges Exper Med* **53** 287, 1926.

²⁰ Petersen, W. F., and Muller, E. F. *The Splanchnoperipheral Balance During Chill and Fever*, *Arch Int Med* **40** 575 (Nov) 1927.

²¹ Muller and Petersen (footnote 14). Muller, E. F. *Evidence of Nervous Control of Leukocytic Activity by Involuntary Nervous System*, *Arch Int Med* **37** 268 (Feb) 1926.

The chill is a manifestation of a pathologic process. Whether or not a similar autonomic control is present during the fine fluctuations of the leukocyte count that take place physiologically is a debatable question. Since the gastro-intestinal tract plays an undoubted rôle in the general autonomic visceral reaction, it may well bear a relation to distribution of leukocytes, and of course, to the fluctuations in the count that take place during physiologic digestion. The stomach is the first part of the tract to be involved in active digestion and probably the portion most actively involved during the period of digestive leukocytosis. Following this train of thought, the conclusion was reached that a possible relation might exist between the tonus of the stomach and the peripheral capillaries and the following experiments were carried out.

EXPERIMENTS

Experiments on Dogs—(1) Leukocyte counts were made on the fasting animal every four or five minutes throughout the period of active hunger contractions.

(2) Leukocytes were counted in the starving animal during active hunger contractions, and the animal was shown food (psychic inhibition of hunger contraction).

(3) Leukocytes were counted in the fed animals with active digestive contractions throughout the period of digestion.

Experiments on Patients—(4) Leukocytes were counted in patients with ulcers throughout the period of active hunger contractions and following the injection of a nonspecific milk preparation intramuscularly.

Method—The dogs were trained to lie perfectly quiet without restraint throughout the experiment. Three of the animals used were gastrostomized three months before the experiment was carried out. A fine rubber balloon was passed into the stomach (by mouth or through fistula) at the end of the duodenal tube. The tube was connected with a water manometer, and the balloon was inflated with 80 cc of air. The fluctuations of the manometer were then recorded on a slowly revolving kymograph.

A similar technic was employed in the patients. They were at complete rest in bed for one hour before and during the course of the experiment. One hundred and twenty cubic centimeters of air was used to inflate the balloon.²²

Leukocyte counts were made at as frequent intervals as seemed necessary under the usual standardized conditions. Blood from the ear was used.

22 I had some difficulty in the beginning in passing this balloon in patients. It was overcome by the following procedure: a few sticks of gelatin to which a little water has been added are heated over a water bath to the melting point. The balloon is dipped in this solution and rapidly twisted with the fingers until it forms practically a straight rod. It is allowed to dry in this position. Should it be necessary, another coat can be applied over the first, in the same manner. The patients experience little difficulty in swallowing this balloon, and when it reaches the stomach the gastric juice readily dissolves off the gelatin. After passing the tube, I waited two or three minutes to permit the gelatin to be removed, the tube was connected with a manometer, and the record taken as in dogs.

Results—EXPERIMENT 1 As the stomach passed into a state of inhibition, following hunger contractions in the fasting animal, the peripheral leukocyte count fell and stayed down during the entire period of inhibition, to rise again as the stomach began to contract (chart 1)

EXPERIMENT 2 During the dilatation of the stomach induced by psychic stimulation in a starving animal, the leukocyte count dropped as the stomach dilated, and returned to its original level only when the stomach began to contract again (chart 2)

EXPERIMENT 3 During the period of digestive contractions, the tonus of the stomach was fairly constant, and similarly, the leukocyte count was constant (chart 3)

EXPERIMENT 4 In patients, the relaxation of tonus in a hungry patient occurring after the intramuscular injection of a nonspecific milk preparation was associated with a considerable leukopenia. Note, however, that this leukopenia became manifest, not at the time of injection, but at the time that the stomach dilated (chart 4)

COMMENT

From these results it would appear that the state of tone of the stomach is associated with distinct fluctuations in the peripheral leukocyte count. However, it is probably not the only factor. For example, it is known that injection of a nonspecific milk preparation, a protein substance, is followed by increased function and capillary dilatation in the liver.²³ I feel, therefore, that the dilation of the stomach which follows the injection of this substance is not a single response, but rather a part of the unified response of the entire splanchnic area.

Further, it is generally known that during active digestion, it is not only the stomach which is stimulated, but the entire splanchnic area.²⁴ If one assumes that the stomach reacts as a representative part of the viscera, one has in that organ a convenient method of determining the reaction of the splanchnic area of stimulation, and further, the relation between the splanchnic area and the peripheral organs. This so-called splanchnoperipheral balance²⁰ is therefore of importance in the controversial points of Widal's hemoclastic crisis. A chronic splanchnic pathologic condition will be associated with hyperemia of the liver, stomach, spleen and other organs, and in turn with catarrhal gastritis and delayed digestion. That means that in such a case the stomach will have to dilate more and longer than the normal stomach to accomplish the same physiologic end. Since gastric dilatation is closely interlinked with peripheral leukopenia the stomach which must dilate the longest will show the longest period of depression of the peripheral leukocyte count (Widal's hemoclastic crisis).

²³ Muller and Petersen (footnote 14, second reference)

²⁴ Ciacci, C, and Pizzini, B. Arch de méd expér et d'anat path **17** 129, 1905

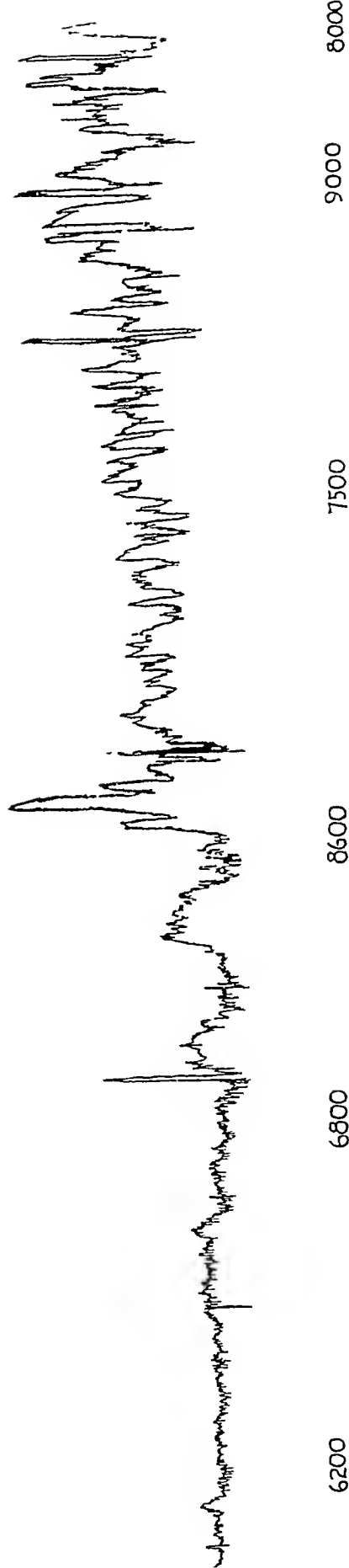


Chart 1 —Fasting animal, low leukocyte count during inhibition, increase of count with beginning contractions

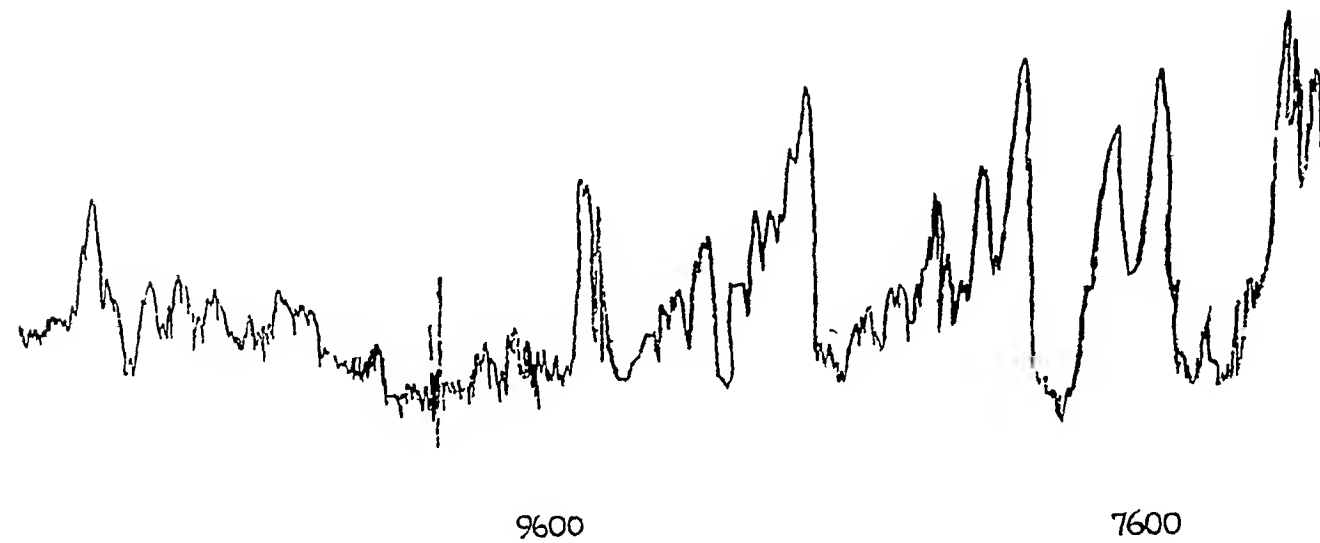
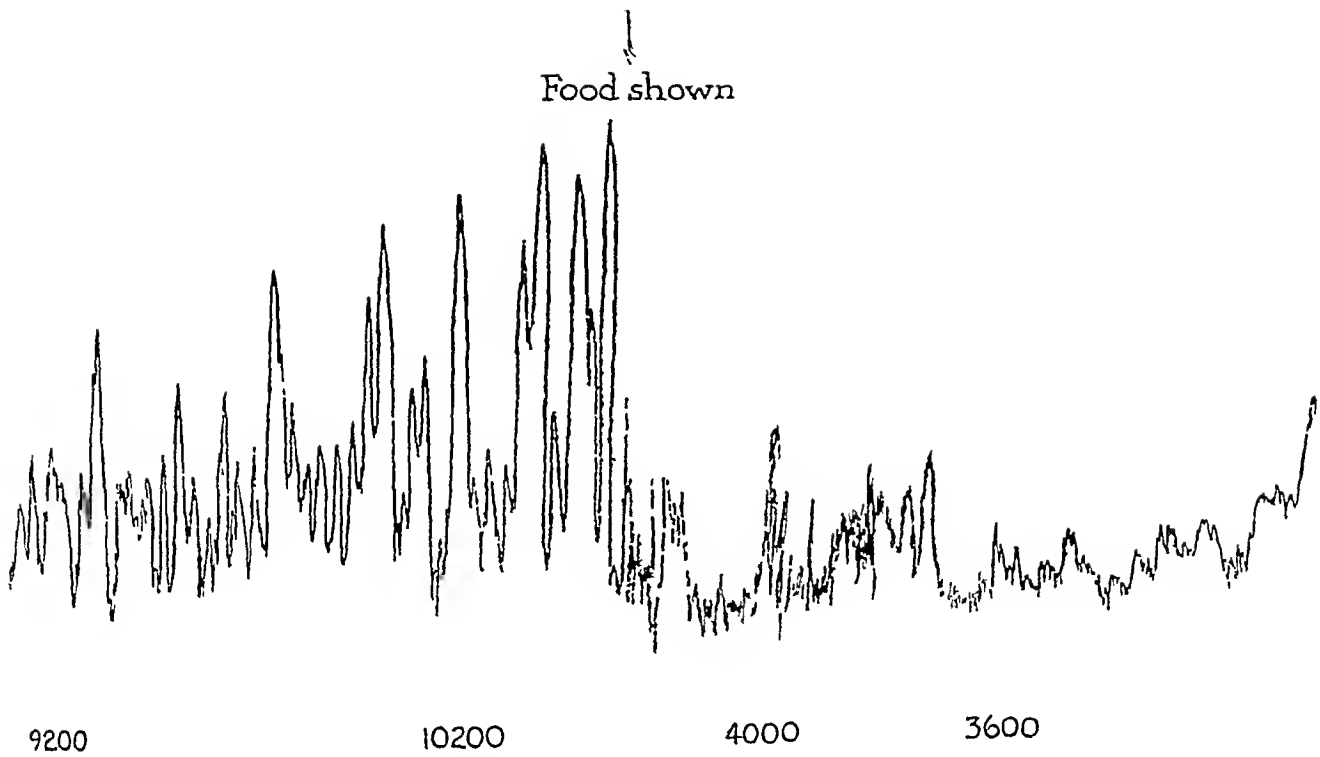
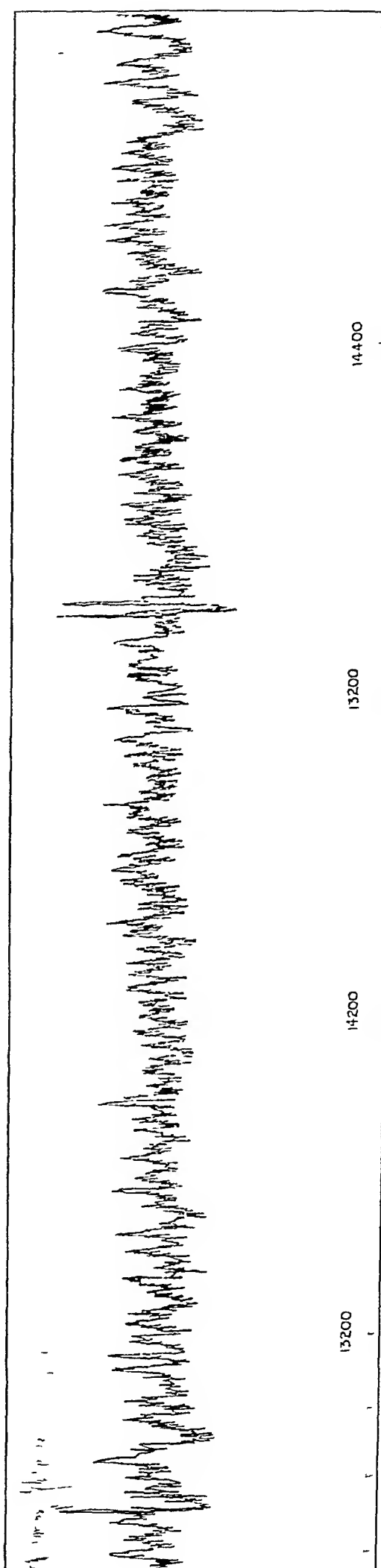
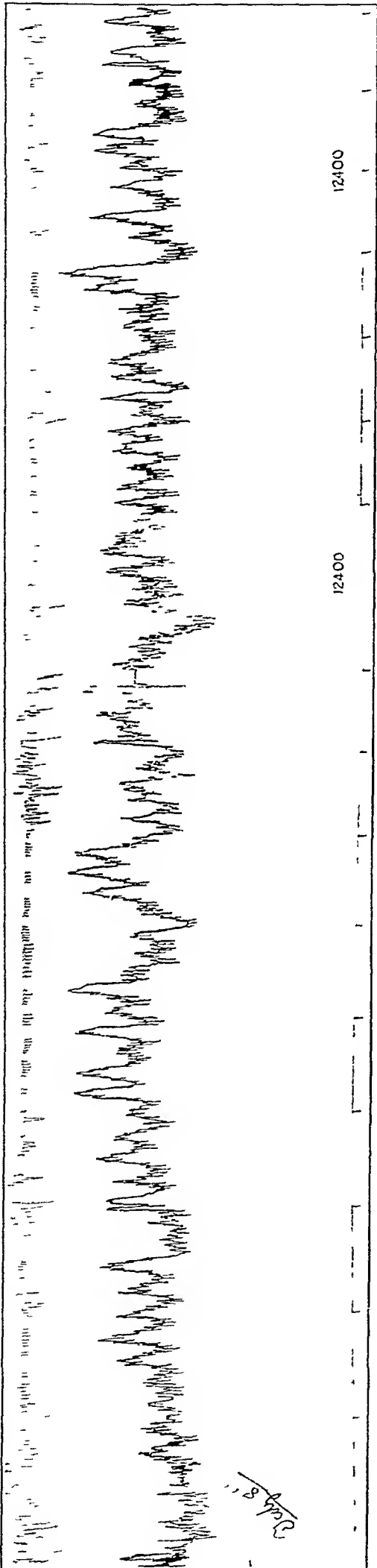


Chart 2—Starving animal, primary period hunger contractions with high peripheral leukocyte count, psychic inhibition following the exhibition of food with immediate effect on the leukocyte count



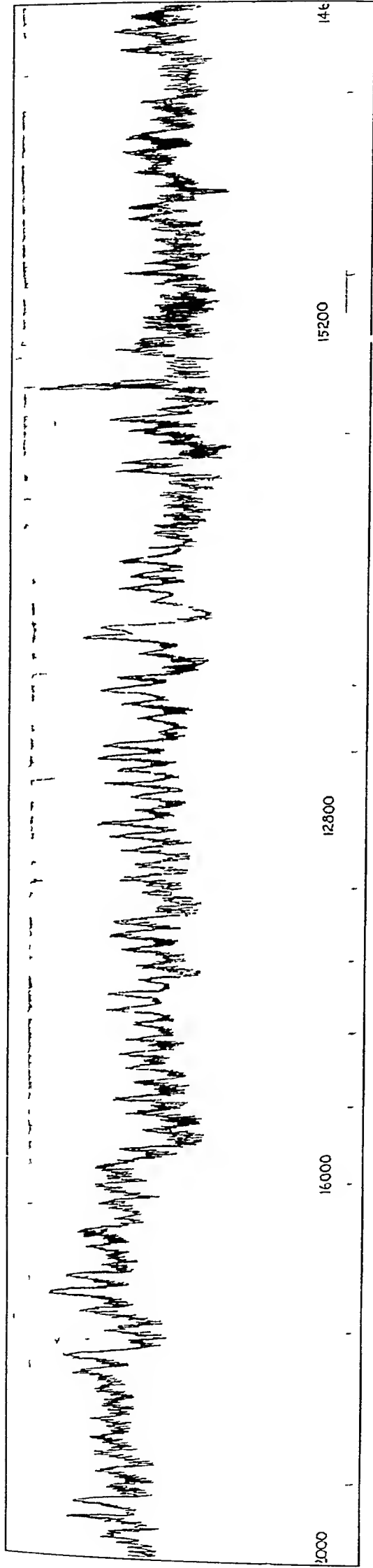
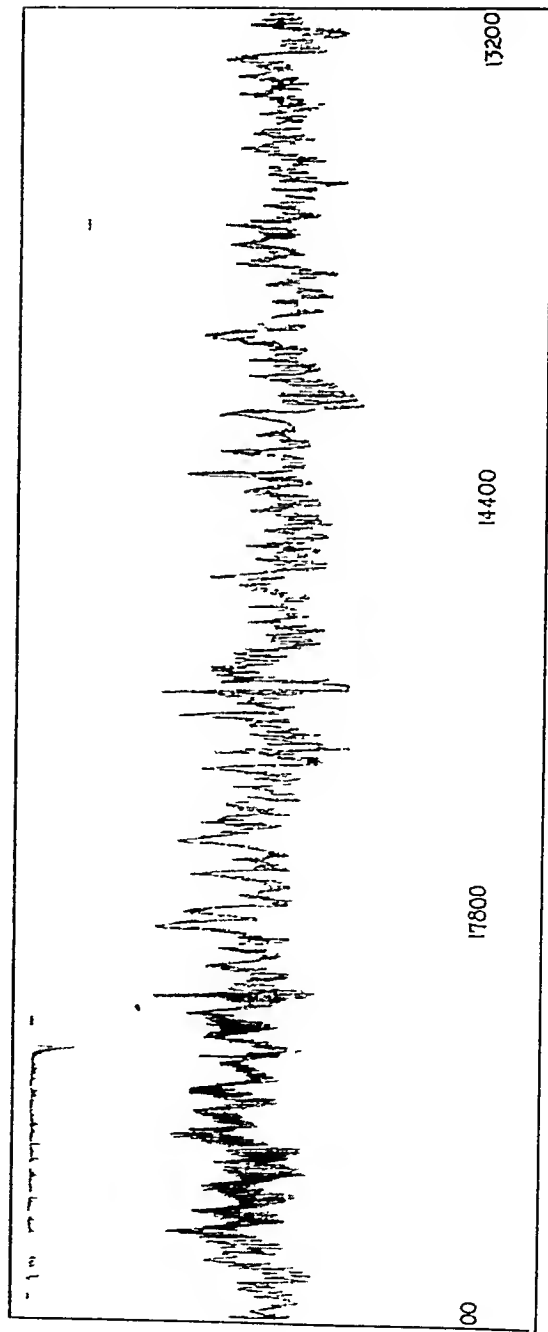
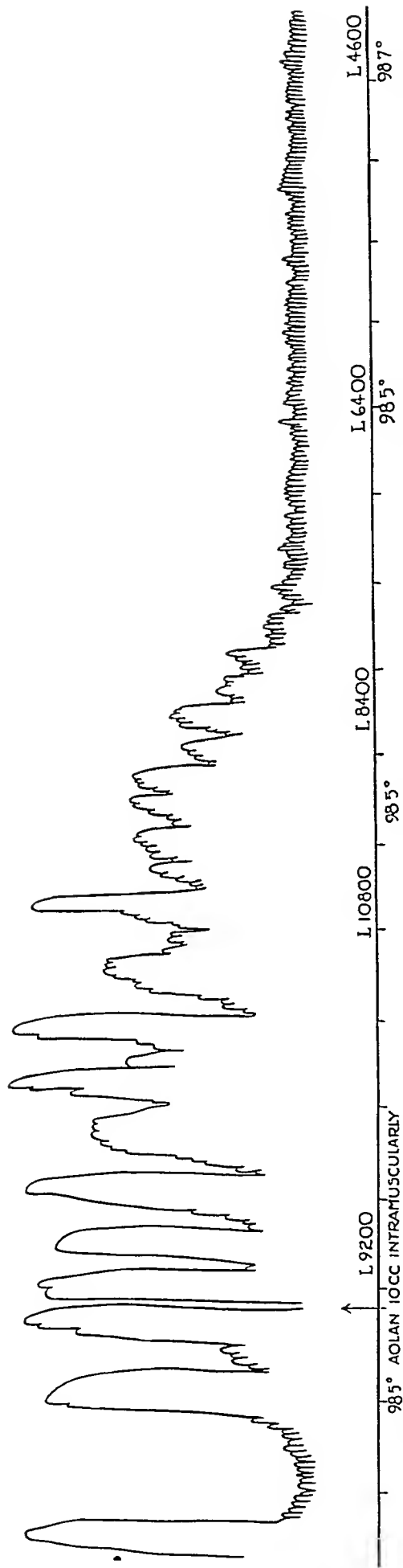


Chart 3—Normal dog during digestive contractions, continued high leukocyte count





• Chart 4 — Patient with gastric ulcer, hunger contractions with relatively high leukocyte count, leukopenia following injection of a nonspecific milk preparation together with coincident inhibition of stomach tonus

Holzer and Schilling¹⁸ have already shown that a typical Widal crisis will appear in every case that shows hypochlorhydria

It would appear, therefore, that not only in liver disease, but in any splanchnic pathologic condition and probably in such diseases that are associated with autonomic imbalance (asthma, hay-fever, hypertension and other conditions), a prolonged leukopenia will follow the ingestion of food—the result of the compensatory dilatation that the stomach must undergo in order to maintain its normal digestive function. At present I am attempting to obtain experimental proof for this hypothesis

SUMMARY

1 There is a distinct time relationship between altered tonus of the stomach and alteration in the peripheral leukocyte count

2 This relation is expressed as a leukocytosis when the stomach is actively contracting and a leukopenia during the period of gastric dilatation

3 In those pathologic states that involve chronic gastric congestion, delayed digestion one would expect a prolonged gastric dilatation to meet the physiologic digestive requirements, and consequently a prolonged leukopenia

4 A discussion concerning how far the balance between the stomach and periphery depends on control through nervous, chemical or mechanical elements is not within the province of this paper

Book Reviews

THE BELOVED PHYSICIAN, SIR JAMES MACKENZIE A BIOGRAPHY By R. MACNAIR WILSON Price, \$4.00 New York The Macmillan Company, 1926

There are many beloved physicians in every generation and Mackenzie well deserved the title for he was loved not only by those who saw in him the helpful physician, but by all who were first attracted by his investigating genius, and who came to know him personally. All these, and all who follow later in the study of medicine will wish to learn all they can of Mackenzie, and will therefore be grateful for this biography. It is to be hoped that they will not be deterred by the strange style the author has cultivated, a combination of girl reporter and bed-time story teller. We get a brief but good account of Mackenzie's descent and early life and schooling, in which William Archer, the translator of Ibsen, appears as a classmate. The author makes much of the fact that Mackenzie was not a keen student in his early days. The impulse to study medicine, it is said, resulted from seeing the colored jars of water in a "chemist's" window—in American, pharmacist's. Mackenzie became an apprentice and for four years worked twelve hours a day in the pharmacy, with fifteen on Saturday and four on Sunday. This would horrify makers of medical school schedules, whose aim is to secure "time to think" for the present day student. Of course, Mackenzie was not formally a medical student then, and yet he had time to learn enough of the practical work and the fascination of the medical career to decide to take up the study, and this intention was not lessened during the year he spent after his apprenticeship, in a Glasgow pharmacy. At 21, he went to Edinburgh to begin medical work, four years older than the majority of the men of his "year." This was in 1874, the year Lister acknowledged his debt to Pasteur. In 1878, when Mackenzie got his degree, Pasteur delivered his address on wound putrefaction, and the young physician, thinking research as revealed by Pasteur was not for him, obtained a position as resident in the Edinburgh Royal Infirmary, as a preparation for general practice. In due time, he settled in the town of Burnley, in the "Black Country," where the first American pilgrims sought him out a few years later. The atmosphere of that Old World corner and the daily routine of Dr. Mackenzie's practice are well set forth by the author. How he took to research by following up the things his curiosity encountered in practice, is described in a provokingly rhetorical style, at least it seems so to a medically trained reader. Just how it affects the intelligent layman would be an interesting thing to investigate. It would be interesting, also, in a seminar in medical history to use the "Beloved Physician," allowing beginners to give their interpretation of the account there, having more advanced students work up Mackenzie's original publications and fitting together the two interpretations. It is unfortunate for medical readers that there is no bibliography. The various lines followed by Mackenzie in his further career are all described by the author, in the same artificial style. Through it all the personality of the man emphasizes itself, showing his power as an observer, a thinker and writer, and as a controversialist, but also his personal charm, a charm both physical and mental, and unusual sincerity and courage.

For the guidance of readers inexperienced in the history of medicine, it should be pointed out that certain exaggerations must be allowed for. The apathy with which Mackenzie's discoveries were received, the opposition he encountered, were not unusual or personal. Auenbrugger, who was no fighter, described the fate of all innovators in a few words. So there is a note of insincerity that Mackenzie, least of all subjects of biography, deserved in the

reiteration of the opposition of "the Giants," that is Mackenzie's seniors in practice, of their "roaring with mirth," of the man who was called a dunce at college, in fact merely called so by himself when at a secondary school. Certain things deserve more detailed mention than the author gives them. Hundreds of men before and after him used Dudgeon's sphygmograph. Some called it a toy and discarded it, some made uncalled for diagnoses on the ground of tracings well or badly made. Many hundreds saw also the motion of the jugular pulse. Mackenzie was almost the first to let his mind play on the phenomena, and was actually the first to employ a modification of the instrument and to advance the knowledge of disorders of the circulation. More might have been said of the apathy of professional investigators of physiology, although in time a few of them gave Mackenzie and the subject valuable assistance. Some of the neglect of simple examinations that Mackenzie complained of undoubtedly resulted from his own destructive criticism. That he had the human tendency to error appears from a quotation in chapter XXXII, in which he asserted that certain variations of the electrocardiogram are beyond interpretation. Perhaps they are, but the Mackenzie who put the funnel over the jugular vein would not have said so, he would have "tried," as he really did, through Thomas Lewis. Still another evidence is seen in his tendency to find "laws" for biologic phenomena, laws that may exist, but that have always eluded those who formally searched for them. The man and his investigations deserve the thoughtful consideration of all who concern themselves with the study of medicine, and the present work, with all its faults, will well repay the reader.

THE PHYSIOLOGY OF EXERCISE A text-book for Students of Physical Education
By JAMES HUFF McCURDY, A M, M D, M P E, Director of Physical Education Course in the International Young Men's Christian Association College, Springfield, Mass., Editor of the American Physical Education Review, Second edition, thoroughly revised. Illustrated. Philadelphia: Lea & Febiger, 1928.

The subtitle of the book more nearly describes the character and aims of the book since it is essentially a textbook for students in physical education rather than a monograph on the physiology of exercise. The first half of the book is devoted to the general effects of exercise on bodily functions such as circulation, blood pressure, heart rate, blood composition, and the effects of exercise in the way of training and neuromuscular mechanism. The second part deals more specifically with the effects of certain types of exercise such as gymnastics, swimming, rowing and running on the bodily functions. There is a chapter on Physical Efficiency Tests and a concluding chapter on the Physiology of Training. Each chapter is concluded with a fairly complete bibliography and a detailed set of questions covering the content of each chapter. These questions appear like elementary examination questions.

The author appears conversant with the literature of the field, but the thorough assimilation in the presentation of the material frequently appears disappointing, the presentation being frequently merely a collection of statements by different authors without much analysis or critical fitting of these into the general scheme of the author. In many places the author appears in the rôle of a propagandist, exhorter or preacher for the benefits of physical training. At times he is guilty of loose or meaningless statements, like the following— "Woman is anabolic, while the man is catabolic in type" "The evolution of the animals has been physical development, that of man largely an intelligent and emotional one." Many of the questions appended at the end of each chapter appear too elementary, if not downright purile, to be included in a textbook on physical training for students of college grade. The following are examples "Put on the board during the class session the normal resting horizontal and standing pulse of each member of the class" "What additional studies in blood pressure need to be made?" "What skeletal muscles are under splanchnic control and why?" "What studies

on the size of the heart in addition to the Harvard studies are needed? 'What are the effects of rowing in future life?'

The author makes a very telling albeit dubious point in favor of rowing by asserting (p 220) "that Harvard oarsmen show a higher percentage of marriage and size of family than all the graduates of Princeton Yale Bowdoin and Harvard. And further "the Harvard oarsmen are above the average in longevity fecundity health and success in life. The Who's Who in America is even brought in as evidence for this superior value of rowing to success. All this is interesting but is it good science?"

Despite these weaknesses or defects in the book, the volume will be found helpful to students of physical education and to doctors in connection with exercise as a therapeutic measure because of the presentation of the essential literature in compact and accessible form.

DISEASES OF THE MOUTH. By STEPLING A. M.F.D. D.D.S. Price \$10. Two hundred and seventy-four illustrations and 29 color plates. St. Louis C. V. Mosby Company, 1927

In his preface the author notes the growing need for a "more intimate co-operation between dentists and physicians. A perusal of the text tends toward the conviction that such consultations are necessary because neither physician nor dentist has the apparatus or experience required by the specialist in any branch of medicine other than his own consequently they must consult with each other and each must record his observations. A review of the chapters on "Examination" points conclusively to the foregoing statements.

The chapter on 'Impacted and Unerupted Teeth' is commendable in that it does not advocate the removal of such teeth without some definite reason for so doing. The judgment of both dentist and physician is frequently required before treatment should be instituted.

The chapter on "Pulpless Teeth" deals with the subject in a rational manner and deprecates treatment by the extraction faddist as well as treatment by those who are opposed to extraction.

In the comprehensive chapter on 'Stomatitis' page 329, I think a correction in priority should be made namely, the term 'Ulceromembranous Gingivitis,' as suggested by Grieves is synonymous with "Acute Ulcerous Gingivitis" described by Dr. Thomas L. Gilmer in a paper published in the Dental Review 1906 volume 19 page 459, and at his suggestion and from material furnished by him Dr. Tunncliffe cultured anaerobically, the organisms discovered and described by Vincent and Plant, thus demonstrating them as the cause of this disease.

This book will prove a valuable addition to the working library of both dentist and physician, as it brings out the multiplicity of diseases manifested in and about the mouth and will greatly assist the diagnostician rather than the surgeon, as the size of the volume probably precludes the full discussion of pathology, technic and after-treatment.

EPIDEMIC INFLUENZA, A SURVEY. By EDWIN O. JORDAN, PH.D. Sc.D., Professor of Hygiene and Bacteriology, The University of Chicago. Price, \$5. Pp 599 with 98 text figures. Chicago American Medical Association, 1927

The Committee on Scientific Research of the American Medical Association is to be congratulated on having secured the services of one so appropriately fitted as Professor Jordan to make a comprehensive survey of the literature on the last great influenza pandemic. He has examined most of the publications on the subject (his selected bibliography contains nearly 1300 references) and has apparently done so with great care. His comments are critical and to the point; his conclusions are drawn with caution.

Jordan believes that the pandemic of 1918 was pretty certainly identical with that of 1890 and the other great pandemics of history, but that its relation

to the endemic disease diagnosed "influenza" and to the milder, more localized interpandemic epidemics of "influenza" is still an open question and is likely to remain so until their etiology is established. The voluminous statistical material on morbidity and mortality and the bearing on them of various social factors is reviewed at some length. The vexing problem of etiology and the rôle played by the secondary invaders are well discussed. Nothing of importance seems to have been added to the old descriptions of the clinical picture of the disease.

The final chapter deals with the various analyses which have been made of the epidemiologic data, and the theories which have been propounded to explain the occurrence of influenza pandemics. Jordan favors the theory of enhanced virulence of the virus as most easily explaining the facts which are at hand.

DIAGNOSIS AND TREATMENT OF DISEASES OF THE STOMACH, WITH AN INTRODUCTION TO PRACTICAL GASTRO-ENTEROLOGY. By MARTIN E. REHFUSS, M.D., Assistant Professor of Medicine at Jefferson Medical College. Cloth. Price, \$12. Pp 1236 with 519 illustrations, some in colors. Philadelphia: W. B. Saunders Company, 1927.

This volume deals entirely with diseases of the stomach and diseases of the gastro-intestinal tract in which definite gastric symptoms occur. The embryology, anatomy and physiology of the organ are considered briefly and in light of recent theories and research. Much of the author's original experimentation is included. Brief chapters are given to the consideration of special diagnostic procedures such as roentgen-ray examination. The consideration of clinical methods of diagnosis is, on the other hand, exhaustive. Several chapters in the book have been contributed by specialists in fields in which the technic or knowledge required for competency necessitates special training or experimentation.

The last half of the volume is given to the pure clinical description of gastric diseases. The author apparently feels the inaccuracy of the terminology employed in classifying many of these diseases. While adhering to the prevalent nomenclature, which as we know is not consistent in many instances with the most recent views in physiology, his consideration of disease is from the physiologic standpoint. These inconsistencies are carefully noted.

The suggested treatment of these diseases is also in concordance with the most recent scientific developments.

The book is recommended to those who desire a clinical treatise on gastric disease, based as far as is possible on scientific method. Certain sections of the book might be more concise. The statistical results following treatment might be considered more fully.

CANCER CONTROL. REPORT OF AN INTERNATIONAL SYMPOSIUM HELD UNDER THE AUSPICES OF THE AMERICAN SOCIETY FOR THE CONTROL OF CANCER, LAKE MOHONK, N. Y., SEPTEMBER 20-24, 1926. Pp 336. Chicago: Surgical Publishing Company, 1927.

This volume of 336 pages represents the opinions of a large number of prominent authorities, both clinicians and laboratory workers, on all phases of the problem of lessening the mortality from cancer. One person in ten today is destined to die of cancer and one in five of those over 45.

Little new knowledge of the disease was reported at this meeting, and the discussions were mainly confined to generalities and problems of educating the laity and the family practitioner in the importance of early diagnosis and radical surgery. Radiotherapy was given but a limited field and then generally in the cases which were otherwise hopeless. The small fields of prevention in such pitifully few cases of cancer the etiology of which is known were dis-

cussed, and other highly controversial material was discussed but was considered unfit for general acceptance

A favorable result in the campaign of the last few years is the increasing number of early curable cases, but much room for improvement is still present. Control by eugenic measures is today theoretically possible but practically out of the question. The lead treatment is too new to pass judgment on but it appears to have great possibilities.

The main accomplishment of the meeting was the organization of world-wide cooperation in the control of cancer.

DIE PHARMAZEUTISCHEN GRUNDLAGEN DER ARZNEIMITTELLEHRE VON GEORG EDMUND DANN. Price, 15 marks. Pp 312 with tables, index and 10 illustrations. Leipzig: Theodor Steinkopff, 1927.

This book is a German edition of Gentz's 'Der vanligare Lakemedelsformerna' subjected to some alterations and made to conform to the German pharmacopoeia. Prescription writing is clearly described and illustrated by numerous examples which demonstrate how practically all of the useful pharmaceutical preparations may be applied in practice. More than half of the book is taken up with worth while tables of dosages, solubilities, incompatibilities, explosive mixtures and so on, the list of antidotes, however, is not entirely modern.

The book is well printed and may be recommended to those interested in this phase of therapeutics.

THE TEXTBOOK OF MEDICINE. By A. S. BILLIMCARTER, M.D. Price, \$3. Pp 530. New York: The MacMillan Company, 1927.

This book is written for nurses. It is well outlined, concise and complete. Only the material essential to the nurse is discussed in any particular disease and enough physiology and pathology is included to make things well understood. The therapy in some cases seems as though it might be a little misleading, as many drugs and procedures are mentioned or discussed which probably are of little value. The book, however, has been carefully written and will rank among the best textbooks for nurses.

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